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(54) Title: EPITOPE SEQUENCES

(57) Abstract: Disclosed herein are polypeptides, including epitopes, clusters, and antigens. Also disclosed are compositions that include said polypeptides and methods for their use.

EPITOPE SEQUENCES

Background of the Invention

Field of the Invention

The present invention generally relates to peptides, and nucleic acids encoding peptides, that are useful epitopes of target-associated antigens. More specifically, the invention relates to epitopes that have a high affinity for MHC class I and that are produced by target-specific proteasomes.

Description of the Related Art

Neoplasia and the Immune System

The neoplastic disease state commonly known as cancer is thought to result generally from a single cell growing out of control. The uncontrolled growth state typically results from a multi-step process in which a series of cellular systems fail, resulting in the genesis of a neoplastic cell. The resulting neoplastic cell rapidly reproduces itself, forms one or more tumors, and eventually may cause the death of the host.

Because the progenitor of the neoplastic cell shares the host's genetic material, neoplastic cells are largely unassailed by the host's immune system. During immune surveillance, the process in which the host's immune system surveys and localizes foreign materials, a neoplastic cell will appear to the host's immune surveillance machinery as a "self" cell.

Viruses and the Immune System

In contrast to cancer cells, virus infection involves the expression of clearly non-self antigens. As a result, many virus infections are successfully dealt with by the immune system with minimal clinical sequela. Moreover, it has been possible to develop effective vaccines for many of those infections that do cause serious disease. A variety of vaccine approaches have been used successfully to combat various diseases. These approaches include subunit vaccines consisting of individual proteins produced through recombinant DNA technology. Notwithstanding these advances, the selection and effective administration of minimal epitopes for use as viral vaccines has remained problematic.

In addition to the difficulties involved in epitope selection stands the problem of viruses that have evolved the capability of evading a host's immune system. Many viruses, especially viruses that establish persistent infections, such as members of the herpes and pox virus families, produce immunomodulatory molecules that permit the virus to evade the host's immune system. The effects of these immunomodulatory molecules on antigen presentation may be overcome by the targeting of select epitopes for administration as immunogenic compositions. To better understand the interaction of neoplastic cells and virally infected cells with the host's immune system, a discussion of the system's components follows below.

The immune system functions to discriminate molecules endogenous to an organism ("self" molecules) from material exogenous or foreign to the organism ("non-self" molecules). The immune system has two types of adaptive responses to foreign bodies based on the components that mediate the response: a humoral response and a cell-mediated response. The humoral response is mediated by antibodies, while the cell-mediated response involves cells classified as lymphocytes. Recent anticancer and antiviral strategies have focused on mobilizing the host immune system as a means of anticancer or antiviral treatment or therapy.

The immune system functions in three phases to protect the host from foreign bodies: the cognitive phase, the activation phase, and the effector phase. In the cognitive phase, the immune system recognizes and signals the presence of a foreign antigen or invader in the body. The foreign antigen can be, for example, a cell surface marker from a neoplastic cell or a viral protein. Once the system is aware of an invading body, antigen specific cells of the immune system proliferate and differentiate in response to the invader-triggered signals. The last stage is the effector stage in which the effector cells of the immune system respond to and neutralize the detected invader.

An array of effector cells implements an immune response to an invader. One type of effector cell, the B cell, generates antibodies targeted against foreign antigens encountered by the host. In combination with the complement system, antibodies direct the destruction of cells or organisms bearing the targeted antigen. Another type of effector cell is the natural killer cell (NK cell), a type of lymphocyte having the capacity to spontaneously recognize and destroy a variety of virus infected cells as well as malignant cell types. The method used by NK cells to recognize target cells is poorly understood.

Another type of effector cell, the T cell, has members classified into three subcategories, each playing a different role in the immune response. Helper T cells secrete cytokines which stimulate the proliferation of other cells necessary for mounting an effective immune response, while suppressor T cells down-regulate the immune response. A third category of T cell, the cytotoxic T cell (CTL), is capable of directly lysing a targeted cell presenting a foreign antigen on its surface.

The Major Histocompatibility Complex and T Cell Target Recognition

T cells are antigen-specific immune cells that function in response to specific antigen signals. B lymphocytes and the antibodies they produce are also antigen-specific entities. However, unlike B lymphocytes, T cells do not respond to antigens in a free or soluble form. For a T cell to respond to an antigen, it requires the antigen to be processed to peptides which are then bound to a presenting structure encoded in the major histocompatibility complex (MHC). This requirement is called "MHC restriction" and it is the mechanism by which T cells differentiate "self" from "non-self" cells. If an antigen is not displayed by a recognizable MHC molecule, the T cell will not recognize and act on the antigen signal. T cells specific for a peptide bound to a

recognizable MHC molecule bind to these MHC-peptide complexes and proceed to the next stages of the immune response.

There are two types of MHC, class I MHC and class II MHC. T Helper cells ($CD4^+$) predominately interact with class II MHC proteins while cytolytic T cells ($CD8^+$) predominately interact with class I MHC proteins. Both classes of MHC protein are transmembrane proteins with a majority of their structure on the external surface of the cell. Additionally, both classes of MHC proteins have a peptide binding cleft on their external portions. It is in this cleft that small fragments of proteins, endogenous or foreign, are bound and presented to the extracellular environment.

Cells called "professional antigen presenting cells" (pAPCs) display antigens to T cells using the MHC proteins but additionally express various co-stimulatory molecules depending on the particular state of differentiation/activation of the pAPC. When T cells, specific for the peptide bound to a recognizable MHC protein, bind to these MHC-peptide complexes on pAPCs, the specific co-stimulatory molecules that act upon the T cell direct the path of differentiation/activation taken by the T cell. That is, the co-stimulation molecules affect how the T cell will act on antigenic signals in future encounters as it proceeds to the next stages of the immune response.

As discussed above, neoplastic cells are largely ignored by the immune system. A great deal of effort is now being expended in an attempt to harness a host's immune system to aid in combating the presence of neoplastic cells in a host. One such area of research involves the formulation of anticancer vaccines.

<u>Anticancer Vaccines</u>

Among the various weapons available to an oncologist in the battle against cancer is the immune system of the patient. Work has been done in various attempts to cause the immune system to combat cancer or neoplastic diseases. Unfortunately, the results to date have been largely disappointing. One area of particular interest involves the generation and use of anticancer vaccines.

To generate a vaccine or other immunogenic composition, it is necessary to introduce to a subject an antigen or epitope against which an immune response may be mounted. Although neoplastic cells are derived from and therefore are substantially identical to normal cells on a genetic level, many neoplastic cells are known to present tumor-associated antigens (TuAAs). In theory, these antigens could be used by a subject's immune system to recognize these antigens and attack the neoplastic cells. In reality, however, neoplastic cells generally appear to be ignored by the host's immune system.

A number of different strategies have been developed in an attempt to generate vaccines with activity against neoplastic cells. These strategies include the use of tumor-associated antigens

as immunogens. For example, U.S. Patent No. 5,993,828, describes a method for producing an immune response against a particular subunit of the Urinary Tumor Associated Antigen by administering to a subject an effective dose of a composition comprising inactivated tumor cells having the Urinary Tumor Associated Antigen on the cell surface and at least one tumor associated antigen selected from the group consisting of GM-2, GD-2, Fetal Antigen and Melanoma Associated Antigen. Accordingly, this patent describes using whole, inactivated tumor cells as the immunogen in an anticancer vaccine.

Another strategy used with anticancer vaccines involves administering a composition containing isolated tumor antigens. In one approach, MAGE-A1 antigenic peptides were used as an immunogen. (See Chaux, P., *et al.*, "Identification of Five MAGE-A1 Epitopes Recognized by Cytolytic T Lymphocytes Obtained by *In Vitro* Stimulation with Dendritic Cells Transduced with MAGE-A1," J. Immunol., 163(5):2928-2936 (1999)). There have been several therapeutic trials using MAGE-A1 peptides for vaccination, although the effectiveness of the vaccination regimes was limited. The results of some of these trials are discussed in Vose, J.M., "Tumor Antigens Recognized by T Lymphocytes," 10th European Cancer Conference, Day 2, Sept. 14, 1999.

In another example of tumor associated antigens used as vaccines, Scheinberg, *et al.* treated 12 chronic myelogenous leukemia (CML) patients already receiving interferon (IFN) or hydroxyurea with 5 injections of class I-associated bcr-abl peptides with a helper peptide plus the adjuvant QS-21. Scheinberg, D.A., *et al.*, "BCR-ABL Breakpoint Derived Oncogene Fusion Peptide Vaccines Generate Specific Immune Responses in Patients with Chronic Myelogenous Leukemia (CML) [Abstract 1665], American Society of Clinical Oncology 35th Annual Meeting, Atlanta (1999). Proliferative and delayed type hypersensitivity (DTH) T cell responses indicative of T-helper activity were elicited, but no cytolytic killer T cell activity was observed within the fresh blood samples.

Additional examples of attempts to identify TuAAs for use as vaccines are seen in the recent work of Cebon, *et al.* and Scheibenbogen, *et al.* Cebon, *et al.* immunized patients with metastatic melanoma using intradermallly administered MART-$1_{26\text{-}35}$ peptide with IL-12 in increasing doses given either subcutaneously or intravenously. Of the first 15 patients, 1 complete remission, 1 partial remission, and 1 mixed response were noted. Immune assays for T cell generation included DTH, which was seen in patients with or without IL-12. Positive CTL assays were seen in patients with evidence of clinical benefit, but not in patients without tumor regression. Cebon, *et al.*, "Phase I Studies of Immunization with Melan-A and IL-12 in HLA A2+ Positive Patients with Stage III and IV Malignant Melanoma," [Abstract 1671], American Society of Clinical Oncology 35th Annual Meeting, Atlanta (1999).

Scheibenbogen, *et al.* immunized 18 patients with 4 HLA class I restricted tyrosinase peptides, 16 with metastatic melanoma and 2 adjuvant patients. Scheibenbogen, *et al.*,

"Vaccination with Tyrosinase peptides and GM-CSF in Metastatic Melanoma: a Phase II Trial," [Abstract 1680], American Society of Clinical Oncology 35th Annual Meeting, Atlanta (1999). Increased CTL activity was observed in 4/15 patients, 2 adjuvant patients, and 2 patients with evidence of tumor regression. As in the trial by Cebon, *et al.*, patients with progressive disease did not show boosted immunity. In spite of the various efforts expended to date to generate efficacious anticancer vaccines, no such composition has yet been developed.

Antiviral Vaccines

Vaccine strategies to protect against viral diseases have had many successes. Perhaps the most notable of these is the progress that has been made against the disease small pox, which has been driven to extinction. The success of the polio vaccine is of a similar magnitude.

Viral vaccines can be grouped into three classifications: live attenuated virus vaccines, such as vaccinia for small pox, the Sabin poliovirus vaccine, and measles mumps and rubella; whole killed or inactivated virus vaccines, such as the Salk poliovirus vaccine, hepatitis A virus vaccine and the typical influenza virus vaccines; and subunit vaccines, such as hepatitis B. Due to their lack of a complete viral genome, subunit vaccines offer a greater degree of safety than those based on whole viruses.

The paradigm of a successful subunit vaccine is the recombinant hepatitis B vaccine based on the viruses envelope protein. Despite much academic interest in pushing the reductionist subunit concept beyond single proteins to individual epitopes, the efforts have yet to bear much fruit. Viral vaccine research has also concentrated on the induction of an antibody response although cellular responses also occur. However, many of the subunit formulations are particularly poor at generating a CTL response.

Summary of the Invention

Previous methods of priming professional antigen presenting cells (pAPCs) to display target cell epitopes have relied simply on causing the pAPCs to express target-associated antigens (TAAs), or epitopes of those antigens which are thought to have a high affinity for MHC I molecules. However, the proteasomal processing of such antigens results in presentation of epitopes on the pAPC that do not correspond to the epitopes present on the target cells.

Using the knowledge that an effective cellular immune response requires that pAPCs present the same epitope that is presented by the target cells, the present invention provides epitopes that have a high affinity for MHC I, and that correspond to the processing specificity of the housekeeping proteasome, which is active in peripheral cells. These epitopes thus correspond to those presented on target cells. The use of such epitopes in compositions, such as vaccines and other immunogenic compositions (including pharmaceutical and immunotherapeutic compositions) can activate the cellular immune response to recognize the correctly processed TAA and can result in removal of target cells that present such epitopes. In some embodiments, the housekeeping

epitopes provided herein can be used in combination with immune epitopes, generating a cellular immune response that is competent to attack target cells both before and after interferon induction. In other embodiments the epitopes are useful in the diagnosis and monitoring of the target-associated disease and in the generation of immunological reagents for such purposes.

Embodiments of the invention relate to isolated epitopes, antigens and/or polypeptides. The isolated antigens and/or polypeptides can include the epitopes. Preferred embodiments include an epitope or antigen having the sequence as disclosed in Tables 1A or 1B. Other embodiments can include an epitope cluster comprising a polypeptide from Tables 1A or 1B. Further, embodiments include a polypeptide having substantial similarity to the already mentioned epitopes, polypeptides, antigens, or clusters. Other preferred embodiments include a polypeptide having functional similarity to any of the above. Still further embodiments relate to a nucleic acid encoding the polypeptide of any of the epitopes, clusters, antigens, and polypeptides from Tables 1A or 1B and mentioned herein.

For purposes of the following summary and discussion of other embodiments of the invention, reference to "the epitope," "the epitopes," or "epitope from Tables 1A or 1B" may include without limitation to all of the foregoing forms of the epitope including an epitope with the sequence set forth in the Tables or elsewhere herein, a cluster comprising such an epitope or epitopes, a polypeptide having substantial or functional similarity to those epitopes or clusters, and the like.

The polypeptide or epitope can be immunologically active. The polypeptide comprising the epitope can be less than about 30 amino acids in length, more preferably, the polypeptide is 8 to 10 amino acids in length, for example. Substantial or functional similarity can include addition of at least one amino acid, for example, and the at least one additional amino acid can be at an N-terminus of the polypeptide. The substantial or functional similarity can include a substitution of at least one amino acid.

The epitope, cluster, or polypeptide comprising the same can have affinity to an HLA-A2 molecule. The affinity can be determined by an assay of binding, by an assay of restriction of epitope recognition, by a prediction algorithm, and the like. The epitope, cluster, or polypeptide comprising the same can have affinity to an HLA-B7, HLA-B51 molecule, and the like.

In preferred embodiments the polypeptide can be a housekeeping epitope. The epitope or polypeptide can correspond to an epitope displayed on a tumor cell, to an epitope displayed on a neovasculature cell, and the like. The epitope or polypeptide can be an immune epitope. The epitope, cluster and/or polypeptide can be a nucleic acid. The epitope, cluster and/or polypeptide can be encoded by a nucleic acid.

Other embodiments relate to compositions, including pharmaceutical or immunogenic compositions comprising the polypeptides, including an epitope from Tables 1A or 1B, a cluster, or

a polypeptide comprising the same, and a pharmaceutically acceptable adjuvant, carrier, diluent, excipient, and the like. The adjuvant can be a polynucleotide. The polynucleotide can include a dinucleotide, which can be CpG, for example. The adjuvant can be encoded by a polynucleotide. The adjuvant can be a cytokine and the cytokine can be, for example, GM-CSF.

The compositions can further include a professional antigen-presenting cell (pAPC). The pAPC can be a dendritic cell, for example. The composition can further include a second epitope. The second epitope can be a polypeptide, a nucleic acid, a housekeeping epitope, an immune epitope, and the like.

Still further embodiments relate to compositions, including pharmaceutical and immunogenic compositions that include any of the nucleic acids discussed herein, including those that encode polypeptides that comprise epitopes or antigens from Tables 1A or 1B. Such compositions can include a pharmaceutically acceptable adjuvant, carrier, diluent, excipient, and the like.

Other embodiments relate to recombinant constructs that include such a nucleic acid as described herein, including those that encode polypeptides that comprise epitopes or antigens from Tables 1A or 1B. The constructs can further include a plasmid, a viral vector, an artificial chromosome, and the like. The construct can further include a sequence encoding at least one feature, such as for example, a second epitope, an IRES, an ISS, an NIS, a ubiquitin, and the like.

Further embodiments relate to purified antibodies that specifically bind to at least one of the epitopes in Tables 1A or 1B. Other embodiments relate to purified antibodies that specifically bind to a peptide-MHC protein complex comprising an epitope disclosed in Tables 1A or 1B or any other suitable epitope. The antibody from any embodiment can be a monoclonal antibody or a polyclonal antibody.

Still other embodiments relate to multimeric MHC-peptide complexes that include an epitope, such as, for example, an epitope disclosed in Tables 1A or 1B. Also, contemplated are antibodies specific for the complexes.

Embodiments relate to isolated T cells expressing a T cell receptor specific for an MHC-peptide complex. The complex can include an epitope, such as, for example, an epitope disclosed in Tables 1A or 1B. The T cell can be produced by an *in vitro* immunization and can be isolated from an immunized animal. Embodiments relate to T cell clones, including cloned T cells, such as those discussed above. Embodiments also relate to polyclonal population of T cells. Such populations can include a T cell, as described above, for example.

Still further embodiments relate to compositions, including pharmaceutical and immunogenic compositions that include a T cell, such as those described above, for example, and a pharmaceutically acceptable adjuvant, carrier, diluent, excipient, and the like.

Embodiments of the invention relate to isolated protein molecules comprising the binding domain of a T cell receptor specific for an MHC-peptide complex. The complex can include an epitope as disclosed in Tables 1A or 1B. The protein can be multivalent. Other embodiments relate to isolated nucleic acids encoding such proteins. Still further embodiments relate to recombinant constructs that include such nucleic acids.

Other embodiments of the invention relate to host cells expressing a recombinant construct as described above and elsewhere herein. The host cells can include constructs encoding an epitope, a cluster or a polypeptide comprising said epitope or said cluster. The epitope or epitope cluster can be one or more of those disclosed in Tables 1A or 1B, for example, and as otherwise defined. The host cell can be a dendritic cell, macrophage, tumor cell, tumor-derived cell, a bacterium, fungus, protozoan, and the like. Embodiments also relate to compositions, including pharmaceutical and immunogenic compositions that include a host cell, such as those discussed herein, and a pharmaceutically acceptable adjuvant, carrier, diluent, excipient, and the like.

Still other embodiments relate to compositions including immunogenic compositions, such as for example, vaccines or immunotherapeutic compositions. The compositions can include at least one component, such as, for example, an epitope disclosed in Tables 1A or 1B or otherwise described herein; a cluster that includes such an epitope, an antigen or polypeptide that includes such an epitope; a composition as described above and herein; a construct as described above and herein, a T cell, a construct comprising a nucleic acid encoding a T cell receptor binding domain specific for an MHC-peptide complex and compositions including the same, a host cell as described above and herein, and compositions comprising the same.

Further embodiments relate to methods of treating an animal. The methods can include administering to an animal a composition, including a pharmaceutical or an immunogenic composition, such as, a vaccine or immunotherapeutic composition, including those disclosed above and herein. The administering step can include a mode of delivery, such as, for example, transdermal, intranodal, perinodal, oral, intravenous, intradermal, intramuscular, intraperitoneal, mucosal, aerosol inhalation, instillation, and the like. The method can further include a step of assaying to determine a characteristic indicative of a state of a target cell or target cells. The method can include a first assaying step and a second assaying step, wherein the first assaying step precedes the administering step, and wherein the second assaying step follows the administering step. The method can further include a step of comparing the characteristic determined in the first assaying step with the characteristic determined in the second assaying step to obtain a result. The result can be for example, evidence of an immune response, a diminution in number of target cells, a loss of mass or size of a tumor comprising target cells, a decrease in number or concentration of an intracellular parasite infecting target cells, and the like.

Embodiments relate to methods of evaluating immunogenicity of a composition, including a vaccine or an immunotherapeutic composition. The methods can include administering to an animal a vaccine or immunotherapeutic, such as those described above and elsewhere herein, and evaluating immunogenicity based on a characteristic of the animal. The animal can be MHC-transgenic.

Other embodiments relate to methods of evaluating immunogenicity that include *in vitro* stimulation of a T cell with the vaccine or immunotherapeutic composition, such as those described above and elsewhere herein, and evaluating immunogenicity based on a characteristic of the T cell. The stimulation can be a primary stimulation.

Still further embodiments relate to methods of making a passive/adoptive immunotherapeutic. The methods can include combining a T cell or a host cell, such as those described above and elsewhere herein, with a pharmaceutically acceptable adjuvant, carrier, diluent, excipient, and the like.

Other embodiments relate to methods of determining specific T cell frequency, and can include the step of contacting T cells with a MHC-peptide complex comprising an epitope disclosed in Tables 1A or 1B, or a complex comprising a cluster or antigen comprising such an epitope. The contacting step can include at least one feature, such as, for example, immunization, restimulation, detection, enumeration, and the like. The method can further include ELISPOT analysis, limiting dilution analysis, flow cytometry, in situ hybridization, the polymerase chain reaction, any combination thereof, and the like.

Embodiments relate to methods of evaluating immunologic response. The methods can include the above-described methods of determining specific T cell frequency carried out prior to and subsequent to an immunization step.

Other embodiments relate to methods of evaluating immunologic response. The methods can include determining frequency, cytokine production, or cytolytic activity of T cells, prior to and subsequent to a step of stimulation with MHC-peptide complexes comprising an epitope, such as, for example an epitope from Tables 1A or 1B, a cluster or a polypeptide comprising such an epitope.

Further embodiments relate to methods of diagnosing a disease. The methods can include contacting a subject tissue with at least one component, including, for example, a T cell, a host cell, an antibody, a protein, including those described above and elsewhere herein; and diagnosing the disease based on a characteristic of the tissue or of the component. The contacting step can take place *in vivo* or *in vitro*, for example.

Still other embodiments relate to methods of making a composition, including for example, a vaccine. The methods can include combining at least one component. For example, the component can be an epitope, a composition, a construct, a T cell, a host cell; including any of

those described above and elsewhere herein, and the like, with a pharmaceutically acceptable adjuvant, carrier, diluent, excipient, and the like.

Embodiments relate to computer readable media having recorded thereon the sequence of any one of SEQ ID NOS: 108-610, in a machine having a hardware or software that calculates the physical, biochemical, immunologic, molecular genetic properties of a molecule embodying said sequence, and the like.

Still other embodiments relate to methods of treating an animal. The methods can include combining the method of treating an animal that includes administering to the animal a vaccine or immunotherapeutic composition, such as described above and elsewhere herein, combined with at least one mode of treatment, including, for example, radiation therapy, chemotherapy, biochemotherapy, surgery, and the like.

Further embodiments relate to isolated polypeptides that include an epitope cluster. In preferred embodiments the cluster can be from a target-associated antigen having the sequence as disclosed in any one of Tables 68-73, wherein the amino acid sequence includes not more than about 80% of the amino acid sequence of the antigen.

Other embodiments relate to immunogenic compositions, including vaccines or immunotherapeutic products that include an isolated peptide as described above and elsewhere herein. Still other embodiments relate to isolated polynucleotides encoding a polypeptide as described above and elsewhere herein. Other embodiments relate vaccines or immunotherapeutic products that include these polynucleotides. The polynucleotide can be DNA, RNA, and the like.

Still further embodiments relate to kits comprising a delivery device and any of the embodiments mentioned above and elsewhere herein. The delivery device can be a catheter, a syringe, an internal or external pump, a reservoir, an inhaler, microinjector, a patch, and any other like device suitable for any route of delivery. As mentioned, the kit, in addition to the delivery device also includes any of the embodiments disclosed herein. For example, without limitations, the kit can include an isolated epitope, a polypeptide, a cluster, a nucleic acid, an antigen, a pharmaceutical composition that includes any of the foregoing, an antibody, a T cell, a T cell receptor, an epitope-MHC complex, a vaccine, an immunotherapeutic, and the like. The kit can also include items such as detailed instructions for use and any other like item.

Brief Description of the Drawings

Figure 1A-1C is a sequence alignment of NY-ESO-1 and several similar protein sequences.

Figure 2 graphically represents a plasmid vaccine backbone useful for delivering nucleic acid-encoded epitopes.

Figures 3A and 3B are FACS profiles showing results of HLA-A2 binding assays for $\text{tyrosinase}_{207\text{-}215}$ and $\text{tyrosinase}_{208\text{-}216}$.

Figure 3C shows cytolytic activity against a tyrosinase epitope by human CTL induced by *in vitro* immunization.

Figure 4 is a T=120 min. time point mass spectrum of the fragments produced by proteasomal cleavage of SSX-2_{31-68}.

Figure 5 shows a binding curve for HLA-A2:SSX-2_{41-49} with controls.

Figure 6 shows specific lysis of SSX-2_{41-49}–pulsed targets by CTL from SSX–2_{41-49}–immunized HLA-A2 transgenic mice.

Figure 7A, B, and C show results of N-terminal pool sequencing of a T=60 min. time point aliquot of the $PSMA_{163-192}$ proteasomal digest.

Figure 8 shows binding curves for HLA-A2:$PSMA_{168-177}$ and HLA-A2:$PSMA_{288-297}$ with controls.

Figure 9 shows results of N-terminal pool sequencing of a T=60 min. time point aliquot of the $PSMA_{281-310}$ proteasomal digest.

Figure 10 shows binding curves for HLA-A2:$PSMA_{461-469}$, HLA-A2:$PSMA_{460-469}$, and HLA-A2:$PSMA_{663-671}$, with controls.

Figure 11 shows the results of a γ (gamma)-IFN-based ELISPOT assay detecting $PSMA_{463-471}$-reactive HLA-$A1^+$ $CD8^+$ T cells.

Figure 12 shows blocking of reactivity of the T cells used in figure 10 by anti-HLA-A1 mAb, demonstrating HLA-A1-restricted recognition.

Figure 13 shows a binding curve for HLA-A2:$PSMA_{663-671}$, with controls.

Figure 14 shows a binding curve for HLA-A2:$PSMA_{662-671}$, with controls.

Figure 15. Comparison of anti-peptide CTL responses following immunization with various doses of DNA by different routes of injection.

Figure 16. Growth of transplanted gp33 expressing tumor in mice immunized by i.ln. injection of gp33 epitope-expressing, or control, plasmid.

Figure 17. Amount of plasmid DNA detected by real-time PCR in injected or draining lymph nodes at various times after i.ln. of i.m. injection, respectively.

Figures 18-70 are proteasomal digestion maps depicting the mapping of mass spectrum peaks from the digest onto the sequence of the indicated substrate.

Detailed Description of the Preferred Embodiment

Definitions

Unless otherwise clear from the context of the use of a term herein, the following listed terms shall generally have the indicated meanings for purposes of this description.

PROFESSIONAL ANTIGEN-PRESENTING CELL (pAPC) – a cell that possesses T cell costimulatory molecules and is able to induce a T cell response. Well characterized pAPCs include dendritic cells, B cells, and macrophages.

PERIPHERAL CELL – a cell that is not a pAPC.

HOUSEKEEPING PROTEASOME – a proteasome normally active in peripheral cells, and generally not present or not strongly active in pAPCs.

IMMUNE PROTEASOME – a proteasome normally active in pAPCs; the immune proteasome is also active in some peripheral cells in infected tissues.

EPITOPE – a molecule or substance capable of stimulating an immune response. In preferred embodiments, epitopes according to this definition include but are not necessarily limited to a polypeptide and a nucleic acid encoding a polypeptide, wherein the polypeptide is capable of stimulating an immune response. In other preferred embodiments, epitopes according to this definition include but are not necessarily limited to peptides presented on the surface of cells, the peptides being non-covalently bound to the binding cleft of class I MHC, such that they can interact with T cell receptors (TCR). Epitopes presented by class I MHC may be in immature or mature form. "Mature" refers to an MHC epitope in distinction to any precursor ("immature") that may include or consist essentially of a housekeeping epitope, but also includes other sequences in a primary translation product that are removed by processing, including without limitation, alone or in any combination proteasomal digestion, N-terminal trimming, or the action of exogenous enzymatic activities. Thus, a mature epitope may be provided embedded in a somewhat longer polypeptide, the immunological potential of which is due, at least in part, to the embedded epitope; or in its ultimate form that can bind in the MHC binding cleft to be recognized by TCR, respectively.

MHC EPITOPE – a polypeptide having a known or predicted binding affinity for a mammalian class I or class II major histocompatibility complex (MHC) molecule.

HOUSEKEEPING EPITOPE – In a preferred embodiment, a housekeeping epitope is defined as a polypeptide fragment that is an MHC epitope, and that is displayed on a cell in which housekeeping proteasomes are predominantly active. In another preferred embodiment, a housekeeping epitope is defined as a polypeptide containing a housekeeping epitope according to the foregoing definition, that is flanked by one to several additional amino acids. In another preferred embodiment, a housekeeping epitope is defined as a nucleic acid that encodes a housekeeping epitope according to the foregoing definitions.

IMMUNE EPITOPE – In a preferred embodiment, an immune epitope is defined as a polypeptide fragment that is an MHC epitope, and that is displayed on a cell in which immune proteasomes are predominantly active. In another preferred embodiment, an immune epitope is defined as a polypeptide containing an immune epitope according to the foregoing definition, that is flanked by one to several additional amino acids. In another preferred embodiment, an immune epitope is defined as a polypeptide including an epitope cluster sequence, having at least two polypeptide sequences having a known or predicted affinity for a class I MHC. In yet another

preferred embodiment, an immune epitope is defined as a nucleic acid that encodes an immune epitope according to any of the foregoing definitions.

TARGET CELL – a cell to be targeted by the vaccines and methods of the invention. Examples of target cells according to this definition include but are not necessarily limited to: a neoplastic cell and a cell harboring an intracellular parasite, such as, for example, a virus, a bacterium, or a protozoan.

TARGET-ASSOCIATED ANTIGEN (TAA) – a protein or polypeptide present in a target cell.

TUMOR-ASSOCIATED ANTIGENS (TuAA) – a TAA, wherein the target cell is a neoplastic cell.

HLA EPITOPE – a polypeptide having a known or predicted binding affinity for a human class I or class II HLA complex molecule.

ANTIBODY – a natural immunoglobulin (Ig), poly- or monoclonal, or any molecule composed in whole or in part of an Ig binding domain, whether derived biochemically or by use of recombinant DNA. Examples include *inter alia,* F(ab), single chain Fv, and Ig variable region-phage coat protein fusions.

ENCODE – an open-ended term such that a nucleic acid encoding a particular amino acid sequence can consist of codons specifying that (poly)peptide, but can also comprise additional sequences either translatable, or for the control of transcription, translation, or replication, or to facilitate manipulation of some host nucleic acid construct.

SUBSTANTIAL SIMILARITY – this term is used to refer to sequences that differ from a reference sequence in an inconsequential way as judged by examination of the sequence. Nucleic acid sequences encoding the same amino acid sequence are substantially similar despite differences in degenerate positions or modest differences in length or composition of any non-coding regions. Amino acid sequences differing only by conservative substitution or minor length variations are substantially similar. Additionally, amino acid sequences comprising housekeeping epitopes that differ in the number of N-terminal flanking residues, or immune epitopes and epitope clusters that differ in the number of flanking residues at either terminus, are substantially similar. Nucleic acids that encode substantially similar amino acid sequences are themselves also substantially similar.

FUNCTIONAL SIMILARITY – this term is used to refer to sequences that differ from a reference sequence in an inconsequential way as judged by examination of a biological or biochemical property, although the sequences may not be substantially similar. For example, two nucleic acids can be useful as hybridization probes for the same sequence but encode differing amino acid sequences. Two peptides that induce cross-reactive CTL responses are functionally similar even if they differ by non-conservative amino acid substitutions (and thus do not meet the substantial similarity definition). Pairs of antibodies, or TCRs, that recognize the same epitope can

be functionally similar to each other despite whatever structural differences exist. In testing for functional similarity of immunogenicity one would generally immunize with the "altered" antigen and test the ability of the elicited response (Ab, CTL, cytokine production, etc.) to recognize the target antigen. Accordingly, two sequences may be designed to differ in certain respects while retaining the same function. Such designed sequence variants are among the embodiments of the present invention.

VACCINE – this term is used to refer to those immunogenic compositions that are capable of eliciting prophylactic and/or therapeutic responses that prevent, cure, or ameliorate disease.

IMMUNOGENIC COMPOSITION - this term is used to refer to compositions capable of inducing an immune response, a reaction, an effect, and/or an event. In some embodiments, such responses, reactions, effects, and/or events can be induced *in vitro* or *in vivo*, for example. Included among these embodiments are the induction, activation, or expansion of cells involved in cell mediated immunity, for example. One example of such cells is cytotoxic T lymphocytes (CTLs). A vaccine is one type of immunogenic composition. Another example of such a composition is one that induces, activates, or expands CTLs *in vitro*. Further examples include pharmaceutical compositions and the like.

Table 1A. SEQ ID NOS.* including epitopes in Examples 1-7, 13, 14.

SEQ ID NO	IDENTITY	SEQUENCE
1	Tyr 207-216	FLPWHRLFLL
2	Tyrosinase protein	Accession number**: P14679
3	SSX-2 protein	Accession number: NP_003138
4	PSMA protein	Accession number: NP_004467
5	Tyrosinase cDNA	Accession number: NM_000372
6	SSX-2 cDNA	Accession number: NM_003147
7	PSMA cDNA	Accession number: NM_004476
8	Tyr 207-215	FLPWHRLFL
9	Tyr 208-216	LPWHRLFLL
10	SSX-2 31-68	YFSKEEWEKMKASEKIFYVYMKRKYEAMTKLGF KATLP
11	SSX-2 32-40	FSKEEWEKM
12	SSX-2 39-47	KMKASEKIF
13	SSX-2 40-48	MKASEKIFY
14	SSX-2 39-48	KMKASEKIFY
15	SSX-2 41-49	KASEKIFYV
16	SSX-2 40-49	MKASEKIFYV
17	SSX-2 41-50	KASEKIFYVY
18	SSX-2 42-49	ASEKIFYVY
19	SSX-2 53-61	RKYEAMTKL
20	SSX-2 52-61	KRKYEAMTKL
21	SSX-2 54-63	KYEAMTKLGF
22	SSX-2 55-63	YEAMTKLGF
23	SSX-2 56-63	EAMTKLGF

SEQ ID NO	IDENTITY	SEQUENCE
24	HBV18-27	FLPSDYFPSV
25	HLA-B44 binder	AEMGKYSFY
26	SSX-1 41-49	KYSEKISYV
27	SSX-3 41-49	KVSEKIVYV
28	SSX-4 41-49	KSSEKIVYV
29	SSX-5 41-49	KASEKIIYV
30	PSMA163-192	AFSPQGMPEGDLVYVNYARTEDFFKLERDM
31	PSMA 168-190	GMPEGDLVYVNYARTEDFFKLER
32	PSMA 169-177	MPEGDLVYV
33	PSMA 168-177	GMPEGDLVYV
34	PSMA 168-176	GMPEGDLVY
35	PSMA 167-176	QGMPEGDLVY
36	PSMA 169-176	MPEGDLVY
37	PSMA 171-179	EGDLVYVNY
38	PSMA 170-179	PEGDLVYVNY
39	PSMA 174-183	LVYVNYARTE
40	PSMA 177-185	VNYARTEDF
41	PSMA 176-185	YVNYARTEDF
42	PSMA 178-186	NYARTEDFF
43	PSMA 179-186	YARTEDFF
44	PSMA 181-189	RTEDFFKLE
45	PSMA 281-310	RGIAEAVGLPSIPVHPIGYYDAQKLLEKMG
46	PSMA 283-307	IAEAVGLPSIPVHPIGYYDAQKLLE
47	PSMA 289-297	LPSIPVHPI
48	PSMA 288-297	GLPSIPVHPI
49	PSMA 297-305	IGYYDAQKL
50	PSMA 296-305	PIGYYDAQKL
51	PSMA 291-299	SIPVHPIGY
52	PSMA 290-299	PSIPVHPIGY
53	PSMA 292-299	IPVHPIGY
54	PSMA 299-307	YYDAQKLLE
55	PSMA454-481	SSIEGNYTLRVDCTPLMYSLVHLTKEL
56	PSMA 456-464	IEGNYTLRV
57	PSMA 455-464	SIEGNYTLRV
58	PSMA 457-464	EGNYTLRV
59	PSMA 461-469	TLRVDCTPL
60	PSMA 460-469	YTLRVDCTPL
61	PSMA 462-470	LRVDCTPLM
62	PSMA 463-471	RVDCTPLMY
63	PSMA 462-471	LRVDCTPLMY
64	PSMA653-687	FDKSNPIVLRMMNDQLMFLERAFIDPLGLPDRPFY
65	PSMA 660-681	VLRMMNDQLMFLERAFIDPLGL
66	PSMA 663-671	MMNDQLMFL
67	PSMA 662-671	RMMNDQLMFL
68	PSMA 662-670	RMMNDQLMF
69	Tyr 1-17	MLLAVLYCLLWSFQTSA
70	GP100 protein[2]	Accession number: P40967
71	MAGE-1 protein	Accession number: P43355
72	MAGE-2 protein	Accession number: P43356

SEQ ID NO	IDENTITY	SEQUENCE
73	MAGE-3 protein	Accession number: P43357
74	NY-ESO-1 protein	Accession number: P78358
75	LAGE-1a protein	Accession number: CAA11116
76	LAGE-1b protein	Accession number: CAA11117
77	PRAME protein	Accession number: NP 006106
78	PSA protein	Accession number: P07288
79	PSCA protein	Accession number: O43653
80	GP100 cds	Accession number: U20093
81	MAGE-1 cds	Accession number: M77481
82	MAGE-2 cds	Accession number: L18920
83	MAGE-3 cds	Accession number: U03735
84	NY-ESO-1 cDNA	Accession number: U87459
85	PRAME cDNA	Accession number: NM_006115
86	PSA cDNA	Accession number: NM_001648
87	PSCA cDNA	Accession number: AF043498
88	CEA protein	Accession number: P06731
89	CEA cDNA	Accession number: NM_004363
90	Her2/Neu protein	Accession number: P04626
91	Her2/Neu cDNA	Accession number: M11730
92	SCP-1 protein	Accession number: Q15431
93	SCP-1 cDNA	Accession number: X95654
94	SSX-4 protein	Accession number: O60224
95	SSX-4 cDNA	Accession number: NM_005636
96	GAGE-1 protein	Accession number: Q13065
97	GAGE-1 cDNA	Accession number: U19142
98	Suvivin protein	Accession number: O15392
99	Survivin cDNA	Accession number: NM_001168
100	Melan-A protein	Accession number: Q16655
101	Melan-A cDNA	Accession number: U06452
102	BAGE protein	Accession number: Q13072
103	BAGE cDNA	Accession number: U19180
104	PSA 59-67	WVLTAAHCI
105	Glandular Kallikrein 1	Accession number: P06870
106	Elastase 2A	Accession number: P08217
107	Pancreatic elastase IIB	Accession number: NP_056933

Table 1B. SEQ ID NOS.* including epitopes in Examples 15-67.

SEQ ID NO	IDENTITY	SEQUENCE
108	Tyr 171-179	NIYDLFVWM
109	Tyr 173-182	YDLFVWMHYY
110	Tyr 174-182	DLFVWMHYY
111	Tyr 186-194	DALLGGSEI
112	Tyr 191-200	GSEIWRDIDF
113	Tyr 192-200	SEIWRDIDF
114	Tyr 193-201	EIWRDIDFA

SEQ ID NO	IDENTITY	SEQUENCE
115	Tyr 407-416	LQEVYPEANA
116	Tyr 409-418	EVYPEANAPI
117	Tyr 410-418	VYPEANAPI
118	Tyr 411-418	YPEANAPI
119	Tyr 411-420	YPEANAPIGH
120	Tyr 416-425	APIGHNRESY
121	Tyr 417-425	PIGHNRESY
122	Tyr 417-426	PIGHNRESYM
123	Tyr 416-425	APIGHNRESY
124	Tyr 417-425	PIGHNRESY
125	Tyr 423-430	ESYMVPFI
126	Tyr 423-432	ESYMVPFIPL
127	Tyr 424-432	SYMVPFIPL
128	Tyr 424-433	SYMVPFIPLY
129	Tyr 425-433	YMVPFIPLY
130	Tyr 426-434	MVPFIPLYR
131	Tyr 426-435	MVPFIPLYRN
132	Tyr 427-434	VPFIPLYR
133	Tyr 430-437	IPLYRNGD
134	Tyr 430-439	IPLYRNGDFF
135	Tyr 431-439	PLYRNGDFF
136	Tyr 431-440	PLYRNGDFFI
137	Tyr 434-443	RNGDFFISSK
138	Tyr 435-443	NGDFFISSK
139	Tyr 463-471	YIKSYLEQA
140	Tyr 466-474	SYLEQASRI
141	Tyr 469-478	EQASRIWSWL
142	Tyr 470-478	QASRIWSWL
143	Tyr 471-478	ASRIWSWL
144	Tyr 471-479	ASRIWSWLL
145	Tyr 473-481	RIWSWLLGA
146	CEA 92-100	GPAYSGREI
147	CEA 92-101	GPAYSGREII
148	CEA 93-100	PAYSGREI
149	CEA 93-101	PAYSGREII
150	CEA 93-102	PAYSGREIIY
151	CEA 94-102	AYSGREIIY
152	CEA 97-105	GREIIYPNA
153	CEA 98-107	REIIYPNASL
154	CEA 99-107	EIIYPNASL
155	CEA 99-108	EIIYPNASLL
156	CEA 100-107	IIYPNASL
157	CEA 100-108	IIYPNASLL
158	CEA 100-109	IIYPNASLLI
159	CEA 102-109	YPNASLLI
160	CEA 107-116	LLIQNIIQND
161	CEA 132-141	EEATGQFRVY
162	CEA 133-141	EATGQFRVY
163	CEA 141-149	YPELPKPSI

SEQ ID NO	IDENTITY	SEQUENCE
164	CEA 142-149	PELPKPSI
165	CEA 225-233	RSDSVILNV
166	CEA 225-234	RSDSVILNVL
167	CEA 226-234	SDSVILNVL
168	CEA 226-235	SDSVILNVLY
169	CEA 227-235	DSVILNVLY
170	CEA 233-242	VLYGPDAPTI
171	CEA 234-242	LYGPDAPTI
172	CEA 235-242	YGPDAPTI
173	CEA 236-245	GPDAPTISPL
174	CEA 237-245	PDAPTISPL
175	CEA 238-245	DAPTISPL
176	CEA 239-247	APTISPLNT
177	CEA 240-249	PTISPLNTSY
178	CEA 241-249	TISPLNTSY
179	CEA 240-249	PTISPLNTSY
180	CEA 241-249	TISPLNTSY
181	CEA 246-255	NTSYRSGENL
182	CEA 247-255	TSYRSGENL
183	CEA 248-255	SYRSGENL
184	CEA 248-257	SYRSGENLNL
185	CEA 249-257	YRSGENLNL
186	CEA 251-259	SGENLNLSC
187	CEA 253-262	ENLNLSCHAA
188	CEA 254-262	NLNLSCHAA
189	CEA 260-269	HAASNPPAQY
190	CEA 261-269	AASNPPAQY
191	CEA 264-273	NPPAQYSWFV
192	CEA 265-273	PPAQYSWFV
193	CEA 266-273	PAQYSWFV
194	CEA 272-280	FVNGTFQQS
195	CEA 310-319	RTTVTTITVY
196	CEA 311-319	TTVTTITVY
197	CEA 319-327	YAEPPKPFI
198	CEA 319-328	YAEPPKPFIT
199	CEA 320-327	AEPPKPFI
200	CEA 321-328	EPPKPFIT
201	CEA 321-329	EPPKPFITS
202	CEA 322-329	PPKPFITS
203	CEA 382-391	SVTRNDVGPY
204	CEA 383-391	VTRNDVGPY
205	CEA 389-397	GPYECGIQN
206	CEA 391-399	YECGIQNEL
207	CEA 394-402	GIQNELSVD
208	CEA 403-411	HSDPVILNV
209	CEA 403-412	HSDPVILNVL
210	CEA 404-412	SDPVILNVL
211	CEA 404-413	SDPVILNVLY
212	CEA 405-412	DPVILNVL

SEQ ID NO	IDENTITY	SEQUENCE
213	CEA 405-413	DPVILNVLY
214	CEA 408-417	ILNVLYGPDD
215	CEA 411-420	VLYGPDDPTI
216	CEA 412-420	LYGPDDPTI
217	CEA 413-420	YGPDDPTI
218	CEA 417-425	DPTISPSYT
219	CEA 418-427	PTISPSYTYY
220	CEA 419-427	TISPSYTYY
221	CEA 418-427	PTISPSYTYY
222	CEA 419-427	TISPSYTYY
223	CEA 419-428	TISPSYTYYR
224	CEA 424-433	YTYYRPGVNL
225	CEA 425-433	TYYRPGVNL
226	CEA 426-433	YYRPGVNL
227	CEA 426-435	YYRPGVNLSL
228	CEA 427-435	YRPGVNLSL
229	CEA 428-435	RPGVNLSL
230	CEA 428-437	RPGVNLSLSC
231	CEA 430-438	GVNLSLSCH
232	CEA 431-440	VNLSLSCHAA
233	CEA 432-440	NLSLSCHAA
234	CEA 438-447	HAASNPPAQY
235	CEA 439-447	AASNPPAQY
236	CEA 442-451	NPPAQYSWLI
237	CEA 443-451	PPAQYSWLI
238	CEA 444-451	PAQYSWLI
239	CEA 449-458	WLIDGNIQQH
240	CEA 450-458	LIDGNIQQH
241	CEA 450-459	LIDGNIQQHT
242	CEA 581-590	RSDPVTLDVL
243	CEA 582-590	SDPVTLDVL
244	CEA 582-591	SDPVTLDVLY
245	CEA 583-590	DPVTLDVL
246	CEA 583-591	DPVTLDVLY
247	CEA 588-597	DVLYGPDTPI
248	CEA 589-597	VLYGPDTPI
249	CEA 596-605	PIISPPDSSY
250	CEA 597-605	IISPPDSSY
251	CEA 597-606	IISPPDSSYL
252	CEA 599-606	SPPDSSYL
253	CEA 600-608	PPDSSYLSG
254	CEA 600-609	PPDSSYLSGA
255	CEA 602-611	DSSYLSGANL
256	CEA 603-611	SSYLSGANL
257	CEA 604-613	SYLSGANLNL
258	CEA 605-613	YLSGANLNL
259	CEA 610-618	NLNLSCHSA
260	CEA 620-629	NPSPQYSWRI
261	CEA 622-629	SPQYSWRI

SEQ ID NO	IDENTITY	SEQUENCE
262	CEA 627-635	WRINGIPQQ
263	CEA 628-636	RINGIPQQH
264	CEA 628-637	RINGIPQQHT
265	CEA 631-639	GIPQQHTQV
266	CEA 632-639	IPQQHTQV
267	CEA 644-653	KITPNNNGTY
268	CEA 645-653	ITPNNNGTY
269	CEA 647-656	PNNNGTYACF
270	CEA 648-656	NNNGTYACF
271	CEA 650-657	NGTYACFV
272	CEA 661-670	ATGRNNSIVK
273	CEA 662-670	TGRNNSIVK
274	CEA 664-672	RNNSIVKSI
275	CEA 666-674	NSIVKSITV
276	GAGE-1 7-16	STYRPRPRRY
277	GAGE-1 8-16	TYRPRPRRY
278	GAGE-1 10-18	RPRPRRYVE
279	GAGE-1 16-23	YVEPPEMI
280	GAGE-1 22-31	MIGPMRPEQF
281	GAGE-1 23-31	IGPMRPEQF
282	GAGE-1 24-31	GPMRPEQF
283	GAGE-1 105-114	KTPEEEMRSH
284	GAGE-1 106-115	TPEEEMRSHY
285	GAGE-1 107-115	PEEEMRSHY
286	GAGE-1 110-119	EMRSHYVAQT
287	GAGE-1 113-121	SHYVAQTGI
288	GAGE-1 115-124	YVAQTGILWL
289	GAGE-1 116-124	VAQTGILWL
290	GAGE-1 116-125	VAQTGILWLL
291	GAGE-1 117-125	AQTGILWLL
292	GAGE-1 118-126	QTGILWLLM
293	GAGE-1 118-127	QTGILWLLMN
294	GAGE-1 120-129	GILWLLMNNC
295	GAGE-1 121-129	ILWLLMNNC
296	GAGE-1 124-131	LLMNNCFL
297	GAGE-1 123-131	WLLMNNCFL
298	GAGE-1 122-130	LWLLMNNCF
299	GAGE-1 121-130	ILWLLMNNCF
300	GAGE-1 121-129	ILWLLMNNC
301	GAGE-1 120-129	GILWLLMNNC
302	GAGE-1 118-127	QTGILWLLMN
303	GAGE-1 118-126	QTGILWLLM
304	GAGE-1 117-125	AQTGILWLL
305	GAGE-1 116-125	VAQTGILWLL
306	GAGE-1 116-124	VAQTGILWL
307	GAGE-1 115-124	YVAQTGILWL
308	GAGE-1 113-121	SHYVAQTGI
309	MAGE-1 62-70	SAFPTTINF
310	MAGE-1 61-70	ASAFPTTINF

SEQ ID NO	IDENTITY	SEQUENCE
311	MAGE-1 60-68	GASAFPTTI
312	MAGE-1 57-66	SPQGASAFPT
313	MAGE-1 144-151	FGKASESL
314	MAGE-1 143-151	IFGKASESL
315	MAGE-1 142-151	EIFGKASESL
316	MAGE-1 142-149	EIFGKASE
317	MAGE-1 133-140	IKNYKHCF
318	MAGE-1 132-140	VIKNYKHCF
319	MAGE-1 131-140	SVIKNYKHCF
320	MAGE-1 132-139	VIKNYKHC
321	MAGE-1 131-139	SVIKNYKHC
322	MAGE-1 128-136	MLESVIKNY
323	MAGE-1 127-136	EMLESVIKNY
324	MAGE-1 126-134	AEMLESVIK
325	MAGE-2 274-283	GPRALIETSY
326	MAGE-2 275-283	PRALIETSY
327	MAGE-2 276-284	RALIETSYV
328	MAGE-2 277-286	ALIETSYVKV
329	MAGE-2 278-286	LIETSYVKV
330	MAGE-2 278-287	LIETSYVKVL
331	MAGE-2 279-287	IETSYVKVL
332	MAGE-2 280-289	ETSYVKVLHH
333	MAGE-2 282-291	SYVKVLHHTL
334	MAGE-2 283-291	YVKVLHHTL
335	MAGE-2 285-293	KVLHHTLKI
336	MAGE-2 303-311	PLHERALRE
337	MAGE-2 302-309	PPLHERAL
338	MAGE-2 301-309	YPPLHERAL
339	MAGE-2 300-309	SYPPLHERAL
340	MAGE-2 299-307	ISYPPLHER
341	MAGE-2 298-307	HISYPPLHER
342	MAGE-2 292-299	KIGGEPHI
343	MAGE-2 291-299	LKIGGEPHI
344	MAGE-2 290-299	TLKIGGEPHI
345	MAGE-3 303-311	PLHEWVLRE
346	MAGE-3 302-309	PPLHEWVL
347	MAGE-3 301-309	YPPLHEWVL
348	MAGE-3 301-308	YPPLHEWV
349	MAGE-3 300-308	SYPPLHEWV
350	MAGE-3 299-308	ISYPPLHEWV
351	MAGE-3 298-307	HISYPPLHEW
352	MAGE-3 293-301	ISGGPHISY
353	MAGE-3 292-301	KISGGPHISY
354	Melan-A 45-54	CWYCRRRNGY
355	Melan-A 46-54	WYCRRRNGY
356	Melan-A 47-55	YCRRRNGYR
357	Melan-A 49-57	RRRNGYRAL
358	Melan-A 51-60	RNGYRALMDK
359	Melan-A 52-60	NGYRALMDK

SEQ ID NO	IDENTITY	SEQUENCE
360	Melan-A 55-63	RALMDKSLH
361	Melan-A 56-63	ALMDKSLH
362	Melan-A 55-64	RALMDKSLHV
363	Melan-A 56-64	ALMDKSLHV
364	PRAME 275-284	YISPEKEEQY
365	PRAME 276-284	ISPEKEEQY
366	PRAME 277-285	SPEKEEQYI
367	PRAME 278-285	PEKEEQYI
368	PRAME 279-288	EKEEQYIAQF
369	PRAME 280-288	KEEQYIAQF
370	PRAME 283-292	QYIAQFTSQF
371	PRAME 284-292	YIAQFTSQF
372	PRAME 284-293	YIAQFTSQFL
373	PRAME 285-293	IAQFTSQFL
374	PRAME 286-295	AQFTSQFLSL
375	PRAME 287-295	QFTSQFLSL
376	PRAME 290-298	SQFLSLQCL
377	PRAME 439-448	VLYPVPLESY
378	PRAME 440-448	LYPVPLESY
379	PRAME 446-455	ESYEDIHGTL
380	PRAME 448-457	YEDIHGTLHL
381	PRAME 449-457	EDIHGTLHL
382	PRAME 451-460	IHGTLHLERL
383	PRAME 454-463	TLHLERLAYL
384	PRAME 455-463	LHLERLAYL
385	PRAME 456-463	HLERLAYL
386	PRAME 456-465	HLERLAYLHA
387	PRAME 458-467	ERLAYLHARL
388	PRAME 459-467	RLAYLHARL
389	PRAME 459-468	RLAYLHARLR
390	PRAME 460-467	LAYLHARL
391	PRAME 460-468	LAYLHARLR
392	PRAME 461-470	AYLHARLREL
393	PRAME 462-470	YLHARLREL
394	PRAME 462-471	YLHARLRELL
395	PRAME 463-471	LHARLRELL
396	PRAME 464-471	HARLRELL
397	PRAME 464-472	HARLRELLC
398	PRAME 469-478	ELLCELGRPS
399	PRAME 470-478	LLCELGRPS
400	PSA 144-153	QEPALGTTCY
401	PSA 145-153	EPALGTTCY
402	PSA 162-171	PEEFLTPKKL
403	PSA 163-171	EEFLTPKKL
404	PSA 165-173	FLTPKKLQC
405	PSA 165-174	FLTPKKLQCV
406	PSA 166-174	LTPKKLQCV
407	PSA 167-174	TPKKLQCV
408	PSA 167-175	TPKKLQCVD

SEQ ID NO	IDENTITY	SEQUENCE
409	PSA 170-179	KLQCVDLHVI
410	PSA 171-179	LQCVDLHVI
411	PSCA 73-81	DSQDYYVGK
412	PSCA 74-82	SQDYYVGKK
413	PSCA 74-83	SQDYYVGKKN
414	PSCA 76-84	DYYVGKKNI
415	PSCA 77-84	YYVGKKNI
416	PSCA 78-86	YVGKKNITC
417	PSCA 78-87	YVGKKNITCC
418	PSMA 381-390	WVFGGIDPQS
419	PSMA 385-394	GIDPQSGAAV
420	PSMA 386-394	IDPQSGAAV
421	PSMA 387-394	DPQSGAAV
422	PSMA 387-395	DPQSGAAVV
423	PSMA 387-396	DPQSGAAVVH
424	PSMA 388-396	PQSGAAVVH
425	PSMA 389-398	QSGAAVVHEI
426	PSMA 390-398	SGAAVVHEI
427	PSMA 391-398	GAAVVHEI
428	PSMA 391-399	GAAVVHEIV
429	PSMA 392-399	AAVVHEIV
430	PSMA 597-605	CRDYAVVLR
431	PSMA 598-607	RDYAVVLRKY
432	PSMA 599-607	DYAVVLRKY
433	PSMA 600-607	YAVVLRKY
434	PSMA 602-611	VVLRKYADKI
435	PSMA 603-611	VLRKYADKI
436	PSMA 603-612	VLRKYADKIY
437	PSMA 604-611	LRKYADKI
438	PSMA 604-612	LRKYADKIY
439	PSMA 605-614	RKYADKIYSI
440	PSMA 606-614	KYADKIYSI
441	PSMA 607-614	YADKIYSI
442	PSMA 616-625	MKHPQEMKTY
443	PSMA 617-625	KHPQEMKTY
444	PSMA 618-627	HPQEMKTYSV
445	SCP-1 62-71	IDSDPALQKV
446	SCP-1 63-71	DSDPALQKV
447	SCP-1 67-76	ALQKVNFLPV
448	SCP-1 70-78	KVNFLPVLE
449	SCP-1 71-80	VNFLPVLEQV
450	SCP-1 72-80	NFLPVLEQV
451	SCP-1 75-84	PVLEQVGNSD
452	SCP-1 76-84	VLEQVGNSD
453	SCP-1 202-210	YEREETRQV
454	SCP-1 202-211	YEREETRQVY
455	SCP-1 203-211	EREETRQVY
456	SCP-1 203-212	EREETRQVYM
457	SCP-1 204-212	REETRQVYM

SEQ ID NO	IDENTITY	SEQUENCE
458	SCP-1 211-220	YMDLNSNIEK
459	SCP-1 213-221	DLNSNIEKM
460	SCP-1 216-226	SNIEKMITAF
461	SCP-1 217-225	NIEKMITAF
462	SCP-1 218-225	IEKMITAF
463	SCP-1 397-406	RLENYEDQLI
464	SCP-1 398-406	LENYEDQLI
465	SCP-1 398-407	LENYEDQLII
466	SCP-1 399-407	ENYEDQLII
467	SCP-1 399-408	ENYEDQLIIL
468	SCP-1 400-408	NYEDQLIIL
469	SCP-1 400-409	NYEDQLIILT
470	SCP-1 401-409	YEDQLIILT
471	SCP-1 401-410	YEDQLIILTM
472	SCP-1 402-410	EDQLIILTM
473	SCP-1 406-415	IILTMELQKT
474	SCP-1 407-415	ILTMELQKT
475	SCP-1 424-432	KLTNNKEVE
476	SCP-1 424-433	KLTNNKEVEL
477	SCP-1 425-433	LTNNKEVEL
478	SCP-1 429-438	KEVELEELKK
479	SCP-1 430-438	EVELEELKK
480	SCP-1 430-439	EVELEELKKV
481	SCP-1 431-439	VELEELKKV
482	SCP-1 530-539	ETSDMTLELK
483	SCP-1 531-539	TSDMTLELK
484	SCP-1 548-556	NKKQEERML
485	SCP-1 553-562	ERMLTQIENL
486	SCP-1 554-562	RMLTQIENL
487	SCP-1 555-562	MLTQIENL
488	SCP-1 555-564	MLTQIENLQE
489	SCP-1 560-569	ENLQETETQL
490	SCP-1 561-569	NLQETETQL
491	SCP-1 561-570	NLQETETQLR
492	SCP-1 567-576	TQLRNELEYV
493	SCP-1 568-576	QLRNELEYV
494	SCP-1 571-580	NELEYVREEL
495	SCP-1 572-580	ELEYVREEL
496	SCP-1 573-580	LEYVREEL
497	SCP-1 574-583	EYVREELKQK
498	SCP-1 575-583	YVREELKQK
499	SCP-1 675-684	LLEEVEKAKV
500	SCP-1 676-684	LEEVEKAKV
501	SCP-1 676-685	LEEVEKAKVI
502	SCP-1 677-685	EEVEKAKVI
503	SCP-1 681-690	KAKVIADEAV
504	SCP-1 683-692	KVIADEAVKL
505	SCP-1 684-692	VIADEAVKL
506	SCP-1 685-692	IADEAVKL

SEQ ID NO	IDENTITY	SEQUENCE
507	SCP-1 694-702	KEIDKRCQH
508	SCP-1 694-703	KEIDKRCQHK
509	SCP-1 695-703	EIDKRCQHK
510	SCP-1 695-704	EIDKRCQHKI
511	SCP-1 696-704	IDKRCQHKI
512	SCP-1 697-704	DKRCQHKI
513	SCP-1 698-706	KRCQHKIAE
514	SCP-1 698-707	KRCQHKIAEM
515	SCP-1 699-707	RCQHKIAEM
516	SCP-1 701-710	QHKIAEMVAL
517	SCP-1 702-710	HKIAEMVAL
518	SCP-1 703-710	KIAEMVAL
519	SCP-1 737-746	QEQSSLRASL
520	SCP-1 738-746	EQSSLRASL
521	SCP-1 739-746	QSSLRASL
522	SCP-1 741-750	SLRASLEIEL
523	SCP-1 742-750	LRASLEIEL
524	SCP-1 743-750	RASLEIEL
525	SCP-1 744-753	ASLEIELSNL
526	SCP-1 745-753	SLEIELSNL
527	SCP-1 745-754	SLEIELSNLK
528	SCP-1 746-754	LEIELSNLK
529	SCP-1 747-755	EIELSNLKA
530	SCP-1 749-758	ELSNLKAELL
531	SCP-1 750-758	LSNLKAELL
532	SCP-1 751-760	SNLKAELLSV
533	SCP-1 752-760	NLKAELLSV
534	SCP-1 752-761	NLKAELLSVK
535	SCP-1 753-761	LKAELLSVK
536	SCP-1 753-762	LKAELLSVKK
537	SCP-1 754-762	KAELLSVKK
538	SCP-1 755-763	AELLSVKKQ
539	SCP-1 787-796	EKKDKKTQTF
540	SCP-1 788-796	KKDKKTQTF
541	SCP-1 789-796	KDKKTQTF
542	SCP-1 797-806	LLETPDIYWK
543	SCP-1 798-806	LETPDIYWK
544	SCP-1 798-807	LETPDIYWKL
545	SCP-1 799-807	ETPDIYWKL
546	SCP-1 800-807	TPDIYWKL
547	SCP-1 809-817	SKAVPSQTV
548	SCP-1 810-817	KAVPSQTV
549	SCP-1 812-821	VPSQTVSRNF
550	SCP-1 815-824	QTVSRNFTSV
551	SCP-1 816-824	TVSRNFTSV
552	SCP-1 816-825	TVSRNFTSVD
553	SCP-1 823-832	SVDHGISKDK
554	SCP-1 829-838	SKDKRDYLWT
555	SCP-1 832-840	KRDYLWTSA

SEQ ID NO	IDENTITY	SEQUENCE
556	SCP-1 832-841	KRDYLWTSAK
557	SCP-1 833-841	RDYLWTSAK
558	SCP-1 835-843	YLWTSAKNT
559	SCP-1 835-844	YLWTSAKNTL
560	SCP-1 837-844	WTSAKNTL
561	SCP-1 841-850	KNTLSTPLPK
562	SCP-1 842-850	NTLSTPLPK
563	SCP-1 832-840	KRDYLWTSA
564	SCP-1 832-841	KRDYLWTSAK
565	SCP-1 833-841	RDYLWTSAK
566	SCP-1 835-843	YLWTSAKNT
567	SCP-1 839-846	SAKNTLST
568	SCP-1 841-850	KNTLSTPLPK
569	SCP-1 842-850	NTLSTPLPK
570	SCP-1 843-852	TLSTPLPKAY
571	SCP-1 844-852	LSTPLPKAY
572	SSX-2 5-12	DAFARRPT
573	SSX-2 7-15	FARRPTVGA
574	SSX-2 8-17	ARRPTVGAQI
575	SSX-2 9-17	RRPTVGAQI
576	SSX-2 10-17	RPTVGAQI
577	SSX-2 13-21	VGAQIPEKI
578	SSX-2 14-21	GAQIPEKI
579	SSX-2 15-24	AQIPEKIQKA
580	SSX-2 16-24	QIPEKIQKA
581	SSX-2 16-25	QIPEKIQKAF
582	SSX-2 17-24	IPEKIQKA
583	SSX-2 17-25	IPEKIQKAF
584	SSX-2 18-25	PEKIQKAF
585	Survivin 116-124	ETNNKKKEF
586	Survivin 117-124	TNNKKKEF
587	Survivin 122-131	KEFEETAKKV
588	Survivin 123-131	EFEETAKKV
589	Survivin 127-134	TAKKVRRA
590	Survivin 126-134	ETAKKVRRA
591	Survivin 128-136	AKKVRRAIE
592	Survivin 129-138	KKVRRAIEQL
593	Survivin 130-138	KVRRAIEQL
594	Survivin 130-139	KVRRAIEQLA
595	Survivin 131-138	VRRAIEQL
596	BAGE 24-31	SPVVSWRL
597	BAGE 21-29	KEESPVVSW
598	BAGE 19-27	LMKEESPVV
599	BAGE 18-27	RLMKEESPVV
600	BAGE 18-26	RLMKEESPV
601	BAGE 14-22	LLQARLMKE
602	BAGE 13-22	QLLQARLMKE
603	Survivin 13-28	FLKDHRISTFKNWPFL
604	Survivin 79-111	KHSSGCAFLSVKKQFEELTLGEFLKLDRERAKN

SEQ ID NO	IDENTITY	SEQUENCE
605	Survivin 130-141	KVRRAIEQLAAM
606	GAGE-1 116-133	VAQTGILWLLMNNCFLNL
607	BAGE 7-17	FLALSAQLLQA
608	BAGE 18-27	RLMKEESPVV
609	BAGE 2-27	AARAVFLALSAQLLQARLMKEESPVV
610	BAGE 30-39	RLEPEDGTAL

*Any of SEQ ID NOS. 108-602 can be useful as epitopes in any of the various embodiments of the invention. Any of SEQ ID NOS. 603-610 can be useful as sequences containing epitopes or epitope clusters, as described in various embodiments of the invention.

**All accession numbers used here and throughout can be accessed through the NCBI databases, for example, through the Entrez seek and retrieval system on the world wide web.

Note that the following discussion sets forth the inventors' understanding of the operation of the invention. However, it is not intended that this discussion limit the patent to any particular theory of operation not set forth in the claims.

In pursuing the development of epitope vaccines others have generated lists of predicted epitopes based on MHC binding motifs. Such peptides can be immunogenic, but may not correspond to any naturally produced antigenic fragment. Therefore, whole antigen will not elicit a similar response or sensitize a target cell to cytolysis by CTL. Therefore such lists do not differentiate between those sequences that can be useful as vaccines and those that cannot. Efforts to determine which of these predicted epitopes are in fact naturally produced have often relied on screening their reactivity with tumor infiltrating lymphocytes (TIL). However, TIL are strongly biased to recognize immune epitopes whereas tumors (and chronically infected cells) will generally present housekeeping epitopes. Thus, unless the epitope is produced by both the housekeeping and immuno- proteasomes, the target cell will generally not be recognized by CTL induced with TIL-identified epitopes. The epitopes of the present invention, in contrast, are generated by the action of a specified proteasome, indicating that they can be naturally produced, and enabling their appropriate use. The importance of the distinction between housekeeping and immune epitopes to vaccine design is more fully set forth in PCT publication WO 01/82963A2. The teachings and embodiments disclosed in said PCT publication are contemplated as supporting principals and embodiments related to and useful in connection with the present invention.

The epitopes of the invention include or encode polypeptide fragments of TAAs that are precursors or products of proteasomal cleavage by a housekeeping or immune proteasome, and that contain or consist of a sequence having a known or predicted affinity for at least one allele of MHC I. In some embodiments, the epitopes include or encode a polypeptide of about 6 to 25 amino acids in length, preferably about 7 to 20 amino acids in length, more preferably about 8 to 15 amino acids in length, and still more preferably 9 or 10 amino acids in length. However, it is understood that the polypeptides can be larger as long as N-terminal trimming can produce the MHC epitope or that

they do not contain sequences that cause the polypeptides to be directed away from the proteasome or to be destroyed by the proteasome. For immune epitopes, if the larger peptides do not contain such sequences, they can be processed in the pAPC by the immune proteasome. Housekeeping epitopes may also be embedded in longer sequences provided that the sequence is adapted to facilitate liberation of the epitope's C-terminus by action of the immunoproteasome. The foregoing discussion has assumed that processing of longer epitopes proceeds through action of the immunoproteasome of the pAPC. However, processing can also be accomplished through the contrivance of some other mechanism, such as providing an exogenous protease activity and a sequence adapted so that action of the protease liberates the MHC epitope. The sequences of these epitopes can be subjected to computer analysis in order to calculate physical, biochemical, immunologic, or molecular genetic properties such as mass, isoelectric point, predicted mobility in electrophoresis, predicted binding to other MHC molecules, melting temperature of nucleic acid probes, reverse translations, similarity or homology to other sequences, and the like.

In constructing the polynucleotides encoding the polypeptide epitopes of the invention, the gene sequence of the associated TAA can be used, or the polynucleotide can be assembled from any of the corresponding codons. For a 10 amino acid epitope this can constitute on the order of 10^6 different sequences, depending on the particular amino acid composition. While large, this is a distinct and readily definable set representing a miniscule fraction of the $>10^{18}$ possible polynucleotides of this length, and thus in some embodiments, equivalents of a particular sequence disclosed herein encompass such distinct and readily definable variations on the listed sequence. In choosing a particular one of these sequences to use in a vaccine, considerations such as codon usage, self-complementarity, restriction sites, chemical stability, etc. can be used as will be apparent to one skilled in the art.

The invention contemplates producing peptide epitopes. Specifically these epitopes are derived from the sequence of a TAA, and have known or predicted affinity for at least one allele of MHC I. Such epitopes are typically identical to those produced on target cells or pAPCs.

Compositions Containing Active Epitopes

Embodiments of the present invention provide polypeptide compositions, including vaccines, therapeutics, diagnostics, pharmacological and pharmaceutical compositions. The various compositions include newly identified epitopes of TAAs, as well as variants of these epitopes. Other embodiments of the invention provide polynucleotides encoding the polypeptide epitopes of the invention. The invention further provides vectors for expression of the polypeptide epitopes for purification. In addition, the invention provides vectors for the expression of the polypeptide epitopes in an APC for use as an anti-tumor vaccine. Any of the epitopes or antigens, or nucleic acids encoding the same, from Table 1 can be used. Other embodiments relate to methods of making and using the various compositions.

A general architecture for a class I MHC-binding epitope can be described, and has been reviewed more extensively in Madden, D.R. *Annu. Rev. Immunol.* 13:587-622, 1995. Much of the binding energy arises from main chain contacts between conserved residues in the MHC molecule and the N- and C-termini of the peptide. Additional main chain contacts are made but vary among MHC alleles. Sequence specificity is conferred by side chain contacts of so-called anchor residues with pockets that, again, vary among MHC alleles. Anchor residues can be divided into primary and secondary. Primary anchor positions exhibit strong preferences for relatively well-defined sets of amino acid residues. Secondary positions show weaker and/or less well-defined preferences that can often be better described in terms of less favored, rather than more favored, residues. Additionally, residues in some secondary anchor positions are not always positioned to contact the pocket on the MHC molecule at all. Thus, a subset of peptides exists that bind to a particular MHC molecule and have a side chain-pocket contact at the position in question and another subset exists that show binding to the same MHC molecule that does not depend on the conformation the peptide assumes in the peptide-binding groove of the MHC molecule. The C-terminal residue (PΩ; omega) is preferably a primary anchor residue. For many of the better studied HLA molecules (e.g. A2, A68, B27, B7, B35, and B53) the second position (P2) is also an anchor residue. However, central anchor residues have also been observed including P3 and P5 in HLA-B8, as well as P5 and PΩ(omega)-3 in the murine MHC molecules H-2D^b and H-2K^b, respectively. Since more stable binding will generally improve immunogenicity, anchor residues are preferably conserved or optimized in the design of variants, regardless of their position.

Because the anchor residues are generally located near the ends of the epitope, the peptide can buckle upward out of the peptide-binding groove allowing some variation in length. Epitopes ranging from 8-11 amino acids have been found for HLA-A68, and up to 13 amino acids for HLA-A2. In addition to length variation between the anchor positions, single residue truncations and extensions have been reported and the N- and C-termini, respectively. Of the non-anchor residues, some point up out of the groove, making no contact with the MHC molecule but being available to contact the TCR, very often P1, P4, and PΩ(omega)-1 for HLA-A2. Others of the non-anchor residues can become interposed between the upper edges of the peptide-binding groove and the TCR, contacting both. The exact positioning of these side chain residues, and thus their effects on binding, MHC fine conformation, and ultimately immunogenicity, are highly sequence dependent. For an epitope to be highly immunogenic it must not only promote stable enough TCR binding for activation to occur, but the TCR must also have a high enough off-rate that multiple TCR molecules can interact sequentially with the same peptide-MHC complex (Kalergis, A.M. et al., *Nature Immunol.* 2:229-234, 2001). Thus, without further information about the ternary complex, both conservative and non-conservative substitutions at these positions merit consideration when designing variants.

The polypeptide epitope variants can be made, for example, using any of the techniques and guidelines for conservative and non-conservative mutations. Variants can be derived from substitution, deletion or insertion of one or more amino acids as compared with the native sequence. Amino acid substitutions can be the result of replacing one amino acid with another amino acid having similar structural and/or chemical properties, such as the replacement of a threonine with a serine, for example. Such replacements are referred to as conservative amino acid replacements, and all appropriate conservative amino acid replacements are considered to be embodiments of one invention. Insertions or deletions can optionally be in the range of about 1 to 4, preferably 1 to 2, amino acids. It is generally preferable to maintain the "anchor positions" of the peptide which are responsible for binding to the MHC molecule in question. Indeed, immunogenicity of peptides can be improved in many cases by substituting more preferred residues at the anchor positions (Franco, et al., *Nature Immunology*, 1(2):145-150, 2000). Immunogenicity of a peptide can also often be improved by substituting bulkier amino acids for small amino acids found in non-anchor positions while maintaining sufficient cross-reactivity with the original epitope to constitute a useful vaccine. The variation allowed can be determined by routine insertions, deletions or substitutions of amino acids in the sequence and testing the resulting variants for activity exhibited by the polypeptide epitope. Because the polypeptide epitope is often 9 amino acids, the substitutions preferably are made to the shortest active epitope, for example, an epitope of 9 amino acids.

Variants can also be made by adding any sequence onto the N-terminus of the polypeptide epitope variant. Such N-terminal additions can be from 1 amino acid up to at least 25 amino acids. Because peptide epitopes are often trimmed by N-terminal exopeptidases active in the pAPC, it is understood that variations in the added sequence can have no effect on the activity of the epitope. In preferred embodiments, the amino acid residues between the last upstream proteasomal cleavage site and the N-terminus of the MHC epitope do not include a proline residue. Serwold, T. at al., Nature Immunol. 2:644-651, 2001. Accordingly, effective epitopes can be generated from precursors larger than the preferred 9-mer class I motif.

Generally, peptides are useful to the extent that they correspond to epitopes actually displayed by MHC I on the surface of a target cell or a pACP. A single peptide can have varying affinities for different MHC molecules, binding some well, others adequately, and still others not appreciably (Table 2). MHC alleles have traditionally been grouped according to serologic reactivity which does not reflect the structure of the peptide-binding groove, which can differ among different alleles of the same type. Similarly, binding properties can be shared across types; groups based on shared binding properties have been termed supertypes. There are numerous alleles of MHC I in the human population; epitopes specific to certain alleles can be selected based on the genotype of the patient.

Table 2.

Predicted Binding of $Tyrosinase_{207-216}$ (SEQ ID NO. 1) to Various MHC types

MHC I type	*Half time of dissociation (min)
A1	0.05
A*0201	1311.
A*0205	50.4
A3	2.7
A*1101 (part of the A3 supertype)	0.012
A24	6.0
B7	4.0
B8	8.0
B14 (part of the B27 supertype)	60.0
B*2702	0.9
B*2705	30.0
B*3501 (part of the B7 supertype)	2.0
B*4403	0.1
B*5101 (part of the B7 supertype)	26.0
B*5102	55.0
B*5801	0.20
B60	0.40
B62	2.0

*HLA Peptide Binding Predictions (world wide web hypertext transfer protocol "access at bimas.dcrt.nih.gov/molbio/hla_bin").

In further embodiments of the invention, the epitope, as peptide or encoding polynucleotide, can be administered as a pharmaceutical composition, such as, for example, a vaccine or an immunogenic composition, alone or in combination with various adjuvants, carriers, or excipients. It should be noted that although the term vaccine may be used throughout the discussion herein, the concepts can be applied and used with any other pharmaceutical composition, including those mentioned herein. Particularly advantageous adjuvants include various cytokines and oligonucleotides containing immunostimulatory sequences (as set forth in greater detail in the co-pending applications referenced herein). Additionally the polynucleotide encoded epitope can be contained in a virus (e.g. *vaccinia* or adenovirus*)* or in a microbial host cell (e.g. S*almonella* or *Listeria monocytogenes*) which is then used as a vector for the polynucleotide (Dietrich, G. et al. Nat. Biotech. 16:181-185, 1998). Alternatively a pAPC can be transformed, *ex vivo*, to express the epitope, or pulsed with peptide epitope, to be itself administered as a vaccine. To increase efficiency of these processes, the encoded epitope can be carried by a viral or bacterial vector, or complexed with a ligand of a receptor found on pAPC. Similarly the peptide epitope can be complexed with or conjugated to a pAPC ligand. A vaccine can be composed of more than a single epitope.

Particularly advantageous strategies for incorporating epitopes and/or epitope clusters, into a vaccine or pharmaceutical composition are disclosed in PCT Publication WO 01/82963 and U.S.

Patent Application No. 09/560,465 entitled "EPITOPE SYNCHRONIZATION IN ANTIGEN PRESENTING CELLS," filed on April 28, 2000. The teaching and embodiments disclosed in said PCT publication are contemplated as supporting principals and embodiments related to and useful in connection with the present invention. Epitope clusters for use in connection with this invention are disclosed in PCT Publication WO 01/82963 and U.S. Patent Application No. 09/561,571 entitled "EPITOPE CLUSTERS," filed on April 28, 2000. The teaching and embodiments disclosed in said PCT publication are contemplated as supporting principals and embodiments related to and useful in connection with the present invention.

Preferred embodiments of the present invention are directed to vaccines and methods for causing a pAPC or population of pAPCs to present housekeeping epitopes that correspond to the epitopes displayed on a particular target cell. Any of the epitopes or antigens in Table 1, can be used for example. In one embodiment, the housekeeping epitope is a TuAA epitope processed by the housekeeping proteasome of a particular tumor type. In another embodiment, the housekeeping epitope is a virus-associated epitope processed by the housekeeping proteasome of a cell infected with a virus. This facilitates a specific T cell response to the target cells. Concurrent expression by the pAPCs of multiple epitopes, corresponding to different induction states (pre- and post-attack), can drive a CTL response effective against target cells as they display either housekeeping epitopes or immune epitopes.

By having both housekeeping and immune epitopes present on the pAPC, this embodiment can optimize the cytotoxic T cell response to a target cell. With dual epitope expression, the pAPCs can continue to sustain a CTL response to the immune-type epitope when the tumor cell switches from the housekeeping proteasome to the immune proteasome with induction by IFN, which, for example, may be produced by tumor-infiltrating CTLs.

In a preferred embodiment, immunization of a patient is with a vaccine that includes a housekeeping epitope. Many preferred TAAs are associated exclusively with a target cell, particularly in the case of infected cells. In another embodiment, many preferred TAAs are the result of deregulated gene expression in transformed cells, but are found also in tissues of the testis, ovaries and fetus. In another embodiment, useful TAAs are expressed at higher levels in the target cell than in other cells. In still other embodiments, TAAs are not differentially expressed in the target cell compare to other cells, but are still useful since they are involved in a particular function of the cell and differentiate the target cell from most other peripheral cells; in such embodiments, healthy cells also displaying the TAA may be collaterally attacked by the induced T cell response, but such collateral damage is considered to be far preferable to the condition caused by the target cell.

The vaccine contains a housekeeping epitope in a concentration effective to cause a pAPC or populations of pAPCs to display housekeeping epitopes. Advantageously, the vaccine can

include a plurality of housekeeping epitopes or one or more housekeeping epitopes optionally in combination with one or more immune epitopes. Formulations of the vaccine contain peptides and/or nucleic acids in a concentration sufficient to cause pAPCs to present the epitopes. The formulations preferably contain epitopes in a total concentration of about 1μg-1mg/100μl of vaccine preparation. Conventional dosages and dosing for peptide vaccines and/or nucleic acid vaccines can be used with the present invention, and such dosing regimens are well understood in the art. In one embodiment, a single dosage for an adult human may advantageously be from about 1 to about 5000 μl of such a composition, administered one time or multiple times, e.g., in 2, 3, 4 or more dosages separated by 1 week, 2 weeks, 1 month, or more. insulin pump delivers 1 ul per hour (lowest frequency) ref intranodal method patent.

The compositions and methods of the invention disclosed herein further contemplate incorporating adjuvants into the formulations in order to enhance the performance of the vaccines. Specifically, the addition of adjuvants to the formulations is designed to enhance the delivery or uptake of the epitopes by the pAPCs. The adjuvants contemplated by the present invention are known by those of skill in the art and include, for example, GMCSF, GCSF, IL-2, IL-12, BCG, tetanus toxoid, osteopontin, and ETA-1.

In some embodiments of the invention, the vaccines can include a recombinant organism, such as a virus, bacterium or parasite, genetically engineered to express an epitope in a host. For example, *Listeria monocytogenes*, a gram-positive, facultative intracellular bacterium, is a potent vector for targeting TuAAs to the immune system. In a preferred embodiment, this vector can be engineered to express a housekeeping epitope to induce therapeutic responses. The normal route of infection of this organism is through the gut and can be delivered orally. In another embodiment, an adenovirus (Ad) vector encoding a housekeeping epitope for a TuAA can be used to induce anti-virus or anti-tumor responses. Bone marrow-derived dendritic cells can be transduced with the virus construct and then injected, or the virus can be delivered directly via subcutaneous injection into an animal to induce potent T-cell responses. Another embodiment employs a recombinant vaccinia virus engineered to encode amino acid sequences corresponding to a housekeeping epitope for a TAA. Vaccinia viruses carrying constructs with the appropriate nucleotide substitutions in the form of a minigene construct can direct the expression of a housekeeping epitope, leading to a therapeutic T cell response against the epitope.

The immunization with DNA requires that APCs take up the DNA and express the encoded proteins or peptides. It is possible to encode a discrete class I peptide on the DNA. By immunizing with this construct, APCs can be caused to express a housekeeping epitope, which is then displayed on class I MHC on the surface of the cell for stimulating an appropriate CTL response. Constructs generally relying on termination of translation or non-proteasomal proteases for generation of proper termini of housekeeping epitopes have been described in PCT Publication

WO 01/82963 and U.S. Patent application No. 09/561,572 entitled EXPRESSION VECTORS ENCODING EPITOPES OF TARGET-ASSOCIATED ANTIGENS, filed on April 28, 2000. The teaching and embodiments disclosed in said PCT publication are contemplated as supporting principals and embodiments related to and useful in connection with the present invention.

As mentioned, it can be desirable to express housekeeping peptides in the context of a larger protein. Processing can be detected even when a small number of amino acids are present beyond the terminus of an epitope. Small peptide hormones are usually proteolytically processed from longer translation products, often in the size range of approximately 60-120 amino acids. This fact has led some to assume that this is the minimum size that can be efficiently translated. In some embodiments, the housekeeping peptide can be embedded in a translation product of at least about 60 amino acids. In other embodiments the housekeeping peptide can be embedded in a translation product of at least about 50, 30, or 15 amino acids.

Due to differential proteasomal processing, the immune proteasome of the pAPC produces peptides that are different from those produced by the housekeeping proteasome in peripheral body cells. Thus, in expressing a housekeeping peptide in the context of a larger protein, it is preferably expressed in the APC in a context other than its full length native sequence, because, as a housekeeping epitope, it is generally only efficiently processed from the native protein by the housekeeping proteasome, which is not active in the APC. In order to encode the housekeeping epitope in a DNA sequence encoding a larger protein, it is useful to find flanking areas on either side of the sequence encoding the epitope that permit appropriate cleavage by the immune proteasome in order to liberate that housekeeping epitope. Altering flanking amino acid residues at the N-terminus and C-terminus of the desired housekeeping epitope can facilitate appropriate cleavage and generation of the housekeeping epitope in the APC. Sequences embedding housekeeping epitopes can be designed *de novo* and screened to determine which can be successfully processed by immune proteasomes to liberate housekeeping epitopes.

Alternatively, another strategy is very effective for identifying sequences allowing production of housekeeping epitopes in APC. A contiguous sequence of amino acids can be generated from head to tail arrangement of one or more housekeeping epitopes. A construct expressing this sequence is used to immunize an animal, and the resulting T cell response is evaluated to determine its specificity to one or more of the epitopes in the array. By definition, these immune responses indicate housekeeping epitopes that are processed in the pAPC effectively. The necessary flanking areas around this epitope are thereby defined. The use of flanking regions of about 4-6 amino acids on either side of the desired peptide can provide the necessary information to facilitate proteasome processing of the housekeeping epitope by the immune proteasome. Therefore, a sequence ensuring epitope synchronization of approximately 16-22 amino acids can be inserted into, or fused to, any protein sequence effectively to result in that

housekeeping epitope being produced in an APC. In alternate embodiments the whole head-to-tail array of epitopes, or just the epitopes immediately adjacent to the correctly processed housekeeping epitope can be similarly transferred from a test construct to a vaccine vector.

In a preferred embodiment, the housekeeping epitopes can be embedded between known immune epitopes, or segments of such, thereby providing an appropriate context for processing. The abutment of housekeeping and immune epitopes can generate the necessary context to enable the immune proteasome to liberate the housekeeping epitope, or a larger fragment, preferably including a correct C-terminus. It can be useful to screen constructs to verify that the desired epitope is produced. The abutment of housekeeping epitopes can generate a site cleavable by the immune proteasome. Some embodiments of the invention employ known epitopes to flank housekeeping epitopes in test substrates; in others, screening as described below are used whether the flanking regions are arbitrary sequences or mutants of the natural flanking sequence, and whether or not knowledge of proteasomal cleavage preferences are used in designing the substrates.

Cleavage at the mature N-terminus of the epitope, while advantageous, is not required, since a variety of N-terminal trimming activities exist in the cell that can generate the mature N-terminus of the epitope subsequent to proteasomal processing. It is preferred that such N-terminal extension be less than about 25 amino acids in length and it is further preferred that the extension have few or no proline residues. Preferably, in screening, consideration is given not only to cleavage at the ends of the epitope (or at least at its C-terminus), but consideration also can be given to ensure limited cleavage within the epitope.

Shotgun approaches can be used in designing test substrates and can increase the efficiency of screening. In one embodiment multiple epitopes can be assembled one after the other, with individual epitopes possibly appearing more than once. The substrate can be screened to determine which epitopes can be produced. In the case where a particular epitope is of concern a substrate can be designed in which it appears in multiple different contexts. When a single epitope appearing in more than one context is liberated from the substrate additional secondary test substrates, in which individual instances of the epitope are removed, disabled, or are unique, can be used to determine which are being liberated and truly constitute sequences ensuring epitope synchronization.

Several readily practicable screens exist. A preferred *in vitro* screen utilizes proteasomal digestion analysis, using purified immune proteasomes, to determine if the desired housekeeping epitope can be liberated from a synthetic peptide embodying the sequence in question. The position of the cleavages obtained can be determined by techniques such as mass spectrometry, HPLC, and N-terminal pool sequencing; as described in greater detail in U. S. Patent Applications entitled METHOD OF EPITOPE DISCOVERY, EPITOPE SYNCHRONIZATION IN ANTIGEN

PRESENTING CELLS, PCT Publication, U.S. applications and Provisional U. S. Patent Applications entitled EPITOPE SEQUENCES.

Alternatively, *in vivo* screens such as immunization or target sensitization can be employed. For immunization a nucleic acid construct capable of expressing the sequence in question is used. Harvested CTL can be tested for their ability to recognize target cells presenting the housekeeping epitope in question. Such targets cells are most readily obtained by pulsing cells expressing the appropriate MHC molecule with synthetic peptide embodying the mature housekeeping epitope. Alternatively, cells known to express housekeeping proteasome and the antigen from which the housekeeping epitope is derived, either endogenously or through genetic engineering, can be used. To use target sensitization as a screen, CTL, or preferably a CTL clone, that recognizes the housekeeping epitope can be used. In this case it is the target cell that expresses the embedded housekeeping epitope (instead of the pAPC during immunization) and it must express immune proteasome. Generally, the target cell can be transformed with an appropriate nucleic acid construct to confer expression of the embedded housekeeping epitope. Loading with a synthetic peptide embodying the embedded epitope using peptide loaded liposomes or a protein transfer reagent such as BIOPORTER™ (Gene Therapy Systems, San Diego, CA) represents an alternative.

Additional guidance on nucleic acid constructs useful as vaccines in accordance with the present invention are disclosed in WO 01/82963 and U.S. Patent Application No. 09/561,572 entitled "EXPRESSION VECTORS ENCODING EPITOPES OF TARGET-ASSOCIATED ANTIGENS," filed on April 28, 2000. Further, expression vectors and methods for their design, which are useful in accordance with the present invention are disclosed in PCT Publication WO 03/063770; U.S. Patent Application No. 10/292,413, filed on November 7, 2002; and U.S. Provisional Application No. 60/336,968 (attorney docket number CTLIMM.022PR) entitled "EXPRESSION VECTORS ENCODING EPITOPES OF TARGET-ASSOCIATED ANTIGENS AND METHODS FOR THEIR DESIGN," filed on 11/7/2001. The teaching and embodiments disclosed in said PCT publications are contemplated as supporting principals and embodiments related to and useful in connection with the present invention.

A preferred embodiment of the present invention includes a method of administering a vaccine including an epitope (or epitopes) to induce a therapeutic immune response. The vaccine is administered to a patient in a manner consistent with the standard vaccine delivery protocols that are known in the art. Methods of administering epitopes of TAAs including, without limitation, transdermal, intranodal, perinodal, oral, intravenous, intradermal, intramuscular, intraperitoneal, and mucosal administration, including delivery by injection, instillation or inhalation. A particularly useful method of vaccine delivery to elicit a CTL response is disclosed in Australian Patent No. 739189 issued January 17, 2002; PCT Publication No. WO 099/02183; U.S. Patent

Application No. 09/380,534, filed on September 1, 1999; a Continuation-in-Part thereof U.S. Patent Application No. 09/776,232 both entitled "A METHOD OF INDUCING A CTL RESPONSE," filed on February 2, 2001, published as 20020007173; and PCT Publication No. WO 02/062368. The teachings and embodiments disclosed in said publications and applications are contemplated as supporting principals and embodiments related to and useful in connection with the present invention.

Reagents Recognizing Epitopes

In another aspect of the invention, proteins with binding specificity for the epitope and/or the epitope-MHC molecule complex are contemplated, as well as the isolated cells by which they can be expressed. In one set of embodiments these reagents take the form of immunoglobulins: polyclonal sera or monoclonal antibodies (mAb), methods for the generation of which are well know in the art. Generation of mAb with specificity for peptide-MHC molecule complexes is known in the art. See, for example, Aharoni et al. *Nature* 351:147-150, 1991; Andersen et al. *Proc. Natl. Acad. Sci. USA* 93:1820-1824, 1996; Dadaglio et al. *Immunity* 6:727-738, 1997; Duc et al. *Int. Immunol.* 5:427-431,1993; Eastman et al. *Eur. J. Immunol.* 26:385-393, 1996; Engberg et al. *Immunotechnology* 4:273-278, 1999; Porgdor et al. *Immunity* 6:715-726, 1997; Puri et al. *J. Immunol.* 158:2471-2476, 1997; and Polakova, K., et al. *J. Immunol.* 165 342-348, 2000.

In other embodiments the compositions can be used to induce and generate, *in vivo* and *in vitro*, T-cells specific for the any of the epitopes and/or epitope-MHC complexes. In preferred embodiments the epitope can be any one or more of those listed in TABLE 1, for example. Thus, embodiments also relate to and include isolated T cells, T cell clones, T cell hybridomas, or a protein containing the T cell receptor (TCR) binding domain derived from the cloned gene, as well as a recombinant cell expressing such a protein. Such TCR derived proteins can be simply the extra-cellular domains of the TCR, or a fusion with portions of another protein to confer a desired property or function. One example of such a fusion is the attachment of TCR binding domains to the constant regions of an antibody molecule so as to create a divalent molecule. The construction and activity of molecules following this general pattern have been reported, for example, Plaksin, D. et al. *J. Immunol.* 158:2218-2227, 1997 and Lebowitz, M.S. et al. *Cell Immunol.* 192:175-184, 1999. The more general construction and use of such molecules is also treated in U.S. patent 5,830,755 entitled T CELL RECEPTORS AND THEIR USE IN THERAPEUTIC AND DIAGNOSTIC METHODS.

The generation of such T cells can be readily accomplished by standard immunization of laboratory animals, and reactivity to human target cells can be obtained by immunizing with human target cells or by immunizing HLA-transgenic animals with the antigen/epitope. For some therapeutic approaches T cells derived from the same species are desirable. While such a cell can be created by cloning, for example, a murine TCR into a human T cell as contemplated above, *in*

vitro immunization of human cells offers a potentially faster option. Techniques for *in vitro* immunization, even using naive donors, are know in the field, for example, Stauss et al., *Proc. Natl. Acad. Sci. USA* 89:7871-7875, 1992; Salgaller et al. *Cancer Res.* 55:4972-4979, 1995; Tsai et al., *J. Immunol.* 158:1796-1802, 1997; and Chung et al., *J. Immunother.* 22:279-287, 1999.

Any of these molecules can be conjugated to enzymes, radiochemicals, fluorescent tags, and toxins, so as to be used in the diagnosis (imaging or other detection), monitoring, and treatment of the pathogenic condition associated with the epitope. Thus a toxin conjugate can be administered to kill tumor cells, radiolabeling can facilitate imaging of epitope positive tumor, an enzyme conjugate can be used in an ELISA-like assay to diagnose cancer and confirm epitope expression in biopsied tissue. In a further embodiment, such T cells as set forth above, following expansion accomplished through stimulation with the epitope and/or cytokines, can be administered to a patient as an adoptive immunotherapy.

<u>Reagents Comprising Epitopes</u>

A further aspect of the invention provides isolated epitope-MHC complexes. In a particularly advantageous embodiment of this aspect of the invention, the complexes can be soluble, multimeric proteins such as those described in U. S. Patent No. 5,635,363 (tetramers) or U. S. Patent No. 6,015,884 (Ig-dimers). Such reagents are useful in detecting and monitoring specific T cell responses, and in purifying such T cells.

Isolated MHC molecules complexed with epitopic peptides can also be incorporated into planar lipid bilayers or liposomes. Such compositions can be used to stimulate T cells *in vitro* or, in the case of liposomes, *in vivo*. Co-stimulatory molecules (e.g. B7, CD40, LFA-3) can be incorporated into the same compositions or, especially for *in vitro* work, co-stimulation can be provided by anti-co-receptor antibodies (e.g. anti-CD28, anti-CD154, anti-CD2) or cytokines (e.g. IL-2, IL-12). Such stimulation of T cells can constitute vaccination, drive expansion of T cells *in vitro* for subsequent infusion in an immuotherapy, or constitute a step in an assay of T cell function.

The epitope, or more directly its complex with an MHC molecule, can be an important constituent of functional assays of antigen-specific T cells at either an activation or readout step or both. Of the many assays of T cell function current in the art (detailed procedures can be found in standard immunological references such as *Current Protocols in Immunology* 1999 John Wiley & Sons Inc., N.Y.) two broad classes can be defined, those that measure the response of a pool of cells and those that measure the response of individual cells. Whereas the former conveys a global measure of the strength of a response, the latter allows determination of the relative frequency of responding cells. Examples of assays measuring global response are cytotoxicity assays, ELISA, and proliferation assays detecting cytokine secretion. Assays measuring the responses of individual cells (or small clones derived from them) include limiting dilution analysis (LDA),

ELISPOT, flow cytometric detection of unsecreted cytokine (described in U.S. Patent No. 5,445,939, entitled "METHOD FOR ASSESSMENT OF THE MONONUCLEAR LEUKOCYTE IMMUNE SYSTEM" and U.S. Patent Nos 5,656,446; and 5,843,689, both entitled "METHOD FOR THE ASSESSMENT OF THE MONONUCLEAR LEUKOCYTE IMMUNE SYSTEM," reagents for which are sold by Becton, Dickinson & Company under the tradename 'FASTIMMUNE') and detection of specific TCR with tetramers or Ig-dimers as stated and referenced above. The comparative virtues of these techniques have been reviewed in Yee, C. et al. *Current Opinion in Immunology*, 13:141–146, 2001. Additionally detection of a specific TCR rearrangement or expression can be accomplished through a variety of established nucleic acid based techniques, particularly in situ and single-cell PCR techniques, as will be apparent to one of skill in the art.

These functional assays are used to assess endogenous levels of immunity, response to an immunologic stimulus (e.g. a vaccine), and to monitor immune status through the course of a disease and treatment. Except when measuring endogenous levels of immunity, any of these assays presume a preliminary step of immunization, whether *in vivo* or *in vitro* depending on the nature of the issue being addressed. Such immunization can be carried out with the various embodiments of the invention described above or with other forms of immunogen (e.g., pAPC-tumor cell fusions) that can provoke similar immunity. With the exception of PCR and tetramer/Ig-dimer type analyses which can detect expression of the cognate TCR, these assays generally benefit from a step of *in vitro* antigenic stimulation which can advantageously use various embodiments of the invention as described above in order to detect the particular functional activity (highly cytolytic responses can sometimes be detected directly). Finally, detection of cytolytic activity requires epitope-displaying target cells, which can be generated using various embodiments of the invention. The particular embodiment chosen for any particular step depends on the question to be addressed, ease of use, cost, and the like, but the advantages of one embodiment over another for any particular set of circumstances will be apparent to one of skill in the art.

The peptide MHC complexes described in this section have traditionally been understood to be non-covalent associations. However it is possible, and can be advantageous, to create a covalent linkages, for example by encoding the epitope and MHC heavy chain or the epitope, ß2-microglobulin, and MHC heavy chain as a single protein (Yu, Y.L.Y., et al., J. Immunol. 168:3145-3149, 2002; Mottez, E., et at., *J. Exp. Med.* 181:493,1995; Dela Cruz, C. S., et al., *Int. Immunol.* 12:1293, 2000; Mage, M. G., et al., *Proc. Natl. Acad. Sci. USA* 89:10658,1992; Toshitani, K., et al., *Proc. Natl. Acad. Sci. USA* 93:236,1996; Lee, L., et al., *Eur. J. Immunol.* 24:2633,1994; Chung, D. H., et al., *J. Immunol.* 163:3699,1999; Uger, R. A. and B. H. Barber, J. Immunol. 160:1598, 1998; Uger, R. A., et al., *J. Immunol.* 162:6024,1999; and White, J., et al., *J. Immunol.* 162:2671, 1999). Such constructs can have superior stability and overcome roadblocks in the processing-

presentation pathway. They can be used in the already described vaccines, reagents, and assays in similar fashion.

Tumor Associated Antigens

Epitopes of the present invention are derived from the TuAAs tyrosinase (SEQ ID NO. 2), SSX-2, (SEQ ID NO. 3), PSMA (prostate-specific membrane antigen) (SEQ ID NO. 4), MAGE-1 (SEQ ID NO. 71), MAGE-2 (SEQ ID NO. 72), MAGE-3 (SEQ ID NO. 73), PRAME, (SEQ ID NO. 77), PSA, (SEQ ID NO. 78), PSCA, (SEQ ID NO. 79), CEA (carcinoembryonic antigen), (SEQ ID NO. 88), SCP-1 (SEQ ID NO. 92), GAGE-1, (SEQ ID NO. 96), survivin, (SEQ ID NO. 98), Melan-A/MART-1 (SEQ ID NO. 100), and BAGE (SEQ ID NO. 102). The natural coding sequences for these fifteen proteins, or any segments within them, can be determined from their cDNA or complete coding (cds) sequences, SEQ ID NOS. 5-7, 81-83, 85-87, 89, 93, 97, 99, 101, and 103, respectively.

Tyrosinase is a melanin biosynthetic enzyme that is considered one of the most specific markers of melanocytic differentiation. Tyrosinase is expressed in few cell types, primarily in melanocytes, and high levels are often found in melanomas. The usefulness of tyrosinase as a TuAA is taught in U.S. Patent 5,747,271 entitled "METHOD FOR IDENTIFYING INDIVIDUALS SUFFERING FROM A CELLULAR ABNORMALITY SOME OF WHOSE ABNORMAL CELLS PRESENT COMPLEXES OF HLA-A2/TYROSINASE DERIVED PEPTIDES, AND METHODS FOR TREATING SAID INDIVIDUALS."

GP100, also known as PMel17, also is a melanin biosynthetic protein expressed at high levels in melanomas. GP100 as a TuAA is disclosed in U.S. Patent 5,844,075 entitled "MELANOMA ANTIGENS AND THEIR USE IN DIAGNOSTIC AND THERAPEUTIC METHODS."

Melan-A, also called MART-1 (Melanoma Antigen Recognized by T cells), is another melanin biosynthetic protein expressed at high levels in melanomas. The usefulness of Melan-A/MART-1 as a TuAA is taught in U.S. Patent Nos. 5,874,560 and 5,994,523 both entitiled "MELANOMA ANTIGENS AND THEIR USE IN DIAGNOSTIC AND THERAPEUTIC METHODS," as well as U.S. Patent No. 5,620,886, entitled "ISOLATED NUCLEIC ACID SEQUENCE CODING FOR A TUMOR REJECTION ANTIGEN PRECURSOR PROCESSED TO AT LEAST ONE TUMOR REJECTION ANTIGEN PRESENTED BY HLA-A2."

SSX-2, also know as Hom-Mel-40, is a member of a family of highly conserved cancer-testis antigens (Gure, A.O. et al. *Int. J. Cancer* 72:965-971, 1997). Its identification as a TuAA is taught in U.S. Patent 6,025,191 entitled "ISOLATED NUCLEIC ACID MOLECULES WHICH ENCODE A MELANOMA SPECIFIC ANTIGEN AND USES THEREOF." Cancer-testis antigens are found in a variety of tumors, but are generally absent from normal adult tissues except testis. Expression of different members of the SSX family have been found variously in tumor cell

lines. Due to the high degree of sequence identity among SSX family members, similar epitopes from more than one member of the family will be generated and able to bind to an MHC molecule, so that some vaccines directed against one member of this family can cross-react and be effective against other members of this family (see example 3 below).

MAGE-1, MAGE-2, and MAGE-3 are members of another family of cancer-testis antigens originally discovered in melanoma (MAGE is a contraction of melanoma-associated antigen) but found in a variety of tumors. The identification of MAGE proteins as TuAAs is taught in U.S. Patent 5,342,774 entitled NUCLEOTIDE SEQUENCE ENCODING THE TUMOR REJECTION ANTIGEN PRECURSOR, MAGE-1, and in numerous subsequent patents. Currently there are 17 entries for (human) MAGE in the SWISS Protein database. There is extensive similarity among these proteins so in many cases, an epitope from one can induce a cross-reactive response to other members of the family. A few of these have not been observed in tumors, most notably MAGE-H1 and MAGE-D1, which are expressed in testes and brain, and bone marrow stromal cells, respectively. The possibility of cross-reactivity on normal tissue is ameliorated by the fact that they are among the least similar to the other MAGE proteins.

GAGE-1 is a member of the GAGE family of cancer testis antigens (Van den Eynde, B., et al., *J. Exp. Med.* 182: 689-698, 1995; U.S Patent Nos. 5,610,013; 5648226; 5,858,689; 6,013,481; and 6,069,001). The PubGene database currently lists 12 distinct accessible members, some of which are synonymously known as PAGE or XAGE. GAGE–1 through GAGE–8 have a very high degree of sequence identity, so most epitopes can be shared among multiple members of the family.

BAGE is a cancer-testis antigen commonly expressed in melanoma, particularly metastatic melanoma, as well as in carcinomas of the lung, breast, bladder, and squamous cells of the head and neck. It's usefulness as a TuAA is taught in U.S. Patent Nos. 5,683,88 entiltled "TUMOR REJECTION ANTIGENS WHICH CORRESPOND TO AMINO ACID SEQUENCES IN TUMOR REJECTION ANTIGEN PRECURSOR BAGE, AND USES THEREOF" and 5,571,711 entitled "ISOLATED NUCLEIC ACID MOLECULES CODING FOR BAGE TUMOR REJECTION ANTIGEN PRECURSORS."

NY-ESO-1, is a cancer-testis antigen found in a wide variety of tumors, also known as CTAG-1 (Cancer-Testis Antigen-1) and CAG-3 (Cancer Antigen-3). NY-ESO-1 as a TuAA is disclosed in U.S. Patent 5,804,381 entitled ISOLATED NUCLEIC ACID MOLECULE ENCODING AN ESOPHAGEAL CANCER ASSOCIATED ANTIGEN, THE ANTIGEN ITSELF, AND USES THEREOF. A paralogous locus encoding antigens with extensive sequence identity, LAGE-1a/s (SEQ ID NO. 75) and LAGE-1b/L (SEQ ID NO. 76), have been disclosed in publicly available assemblies of the human genome , and have been concluded to arise through alternate splicing. Additionally, CT-2 (or CTAG-2, Cancer-Testis Antigen-2) appears to be either an allele, a mutant, or a sequencing discrepancy of LAGE-1b/L. Due to the extensive sequence identity,

many epitopes from NY-ESO-1 can also induce immunity to tumors expressing these other antigens. See figure 1. The proteins are virtually identical through amino acid 70. From 71-134 the longest run of identities between NY-ESO-1 and LAGE is 6 residues, but potentially cross-reactive sequences are present. And from 135-180 NY-ESO and LAGE-1a/s are identical except for a single residue, but LAGE-1b/L is unrelated due to the alternate splice. The CAMEL and LAGE-2 antigens appear to derive from the LAGE-1 mRNA, but from alternate reading frames, thus giving rise to unrelated protein sequences. More recently, GenBank Accession AF277315.5, Homo sapiens chromosome X clone RP5-865E18, RP5-1087L19, complete sequence, reports three independent loci in this region which are labeled as LAGE1 (corresponding to CTAG-2 in the genome assemblies), plus LAGE2-A and LAGE2-B (both corresponding to CTAG-1 in the genome assemblies).

PSMA (prostate-specific membranes antigen), a TuAA described in U.S. Patent 5,538,866 entitled "PROSTATE-SPECIFIC MEMBRANES ANTIGEN", is expressed by normal prostate epithelium and, at a higher level, in prostatic cancer. It has also been found in the neovasculature of non-prostatic tumors. PSMA can thus form the basis for vaccines directed to both prostate cancer and to the neovasculature of other tumors. This later concept is more fully described in U.S. Patent Publication No. 20030046714; PCT Publication No. WO 02/069907; and a provisional U.S. Patent application No. 60/274,063 entitled ANTI-NEOVASCULAR VACCINES FOR CANCER, filed March 7, 2001, and U.S. Application No. 10/094,699, attorney docket number CTLIMM.015A, filed on March 7, 2002, entitled "ANTI-NEOVASCULAR PREPARATIONS FOR CANCER." The teachings and embodiments disclosed in said publications and applications are contemplated as supporting principals and embodiments related to and useful in connection with the present invention. Briefly, as tumors grow they recruit ingrowth of new blood vessels. This is understood to be necessary to sustain growth as the centers of unvascularized tumors are generally necrotic and angiogenesis inhibitors have been reported to cause tumor regression. Such new blood vessels, or neovasculature, express antigens not found in established vessels, and thus can be specifically targeted. By inducing CTL against neovascular antigens the vessels can be disrupted, interrupting the flow of nutrients to (and removal of wastes from) tumors, leading to regression.

Alternate splicing of the PSMA mRNA also leads to a protein with an apparent start at Met_{58}, thereby deleting the putative membrane anchor region of PSMA as described in U.S. Patent 5,935,818 entitled "ISOLATED NUCLEIC ACID MOLECULE ENCODING ALTERNATIVELY SPLICED PROSTATE-SPECIFIC MEMBRANES ANTIGEN AND USES THEREOF." A protein termed PSMA-like protein, Genbank accession number AF261715, is nearly identical to amino acids 309-750 of PSMA and has a different expression profile. Thus the most preferred epitopes are those with an N-terminus located from amino acid 58 to 308.

PRAME, also know as MAPE, DAGE, and OIP4, was originally observed as a melanoma antigen. Subsequently, it has been recognized as a CT antigen, but unlike many CT antigens (e.g., MAGE, GAGE, and BAGE) it is expressed in acute myeloid leukemias. PRAME is a member of the MAPE family which consists largely of hypothetical proteins with which it shares limited sequence similarity. The usefulness of PRAME as a TuAA is taught in U.S. Patent 5,830,753 entitled "ISOLATED NUCLEIC ACID MOLECULES CODING FOR TUMOR REJECTION ANTIGEN PRECURSOR DAGE AND USES THEREOF."

PSA, prostate specific antigen, is a peptidase of the kallikrein family and a differentiation antigen of the prostate. Expression in breast tissue has also been reported. Alternate names include gamma-seminoprotein, kallikrein 3, seminogelase, seminin, and P-30 antigen. PSA has a high degree of sequence identity with the various alternate splicing products prostatic/glandular kallikrein–1 and –2, as well as kalikrein 4, which is also expressed in prostate and breast tissue. Other kallikreins generally share less sequence identity and have different expression profiles. Nonetheless, cross-reactivity that might be provoked by any particular epitope, along with the likelihood that that epitope would be liberated by processing in non-target tissues (most generally by the housekeeping proteasome), should be considered in designing a vaccine.

PSCA, prostate stem cell antigen, and also known as SCAH-2, is a differentiation antigen preferentially expressed in prostate epithelial cells, and overexpresssed in prostate cancers. Lower level expression is seen in some normal tissues including neuroendocrine cells of the digestive tract and collecting ducts of the kidney. PSCA is described in U.S. Patent 5,856,136 entitled "HUMAN STEM CELL ANTIGENS."

Synaptonemal complex protein 1 (SCP-1), also known as HOM-TES-14, is a meiosis-associated protein and also a cancer-testis antigen (Tureci, O., et al. Proc. Natl. Acad. Sci. USA 95:5211-5216, 1998). As a cancer antigen its expression is not cell-cycle regulated and it is found frequently in gliomas, breast, renal cell, and ovarian carcinomas. It has some similarity to myosins, but with few enough identities that cross-reactive epitopes are not an immediate prospect.

The ED-B domain of fibronectin is also a potential target. Fibronectin is subject to developmentally regulated alternative splicing, with the ED-B domain being encoded by a single exon that is used primarily in oncofetal tissues (Matsuura, H. and S. Hakomori *Proc. Natl. Acad. Sci. USA* 82:6517-6521, 1985; Carnemolla, B. et al. *J. Cell Biol.* 108:1139-1148, 1989; Loridon-Rosa, B. et al. *Cancer Res.*50:1608-1612, 1990; Nicolo, G. et al. *Cell Differ. Dev.* 32:401-408, 1990; Borsi, L. et al. *Exp. Cell Res.* 199:98-105, 1992; Oyama, F. et al. *Cancer Res.* 53:2005-2011, 1993; Mandel, U. et al. *APMIS* 102:695-702, 1994; Farnoud, M.R. et al. *Int. J. Cancer* 61:27-34, 1995; Pujuguet, P. et al. Am. J. Pathol. 148:579-592, 1996; Gabler, U. et al. *Heart* 75:358-362, 1996;Chevalier, X. *Br. J. Rheumatol.* 35:407-415, 1996; Midulla, M. *Cancer Res.* 60:164-169, 2000).

The ED-B domain is also expressed in fibronectin of the neovasculature (Kaczmarek, J. et al. *Int. J. Cancer* 59:11-16, 1994; Castellani, P. et al. *Int. J. Cancer* 59:612-618, 1994; Neri, D. et al. *Nat. Biotech.* 15:1271-1275, 1997; Karelina, T.V. and A.Z. Eisen *Cancer Detect. Prev.* 22:438-444, 1998; Tarli, L. et al. *Blood* 94:192-198, 1999; Castellani, P. et al. *Acta Neurochir. (Wien)* 142:277-282, 2000). As an oncofetal domain, the ED-B domain is commonly found in the fibronectin expressed by neoplastic cells in addition to being expressed by the neovasculature. Thus, CTL-inducing vaccines targeting the ED-B domain can exhibit two mechanisms of action: direct lysis of tumor cells, and disruption of the tumor's blood supply through destruction of the tumor-associated neovasculature. As CTL activity can decay rapidly after withdrawal of vaccine, interference with normal angiogenesis can be minimal. The design and testing of vaccines targeted to neovasculature is described in Provisional U.S. Patent Application No. 60/274,063 entitled "ANTI-NEOVASCULATURE VACCINES FOR CANCER" and in U.S. Patent Application No. 10/094,699, attorney docket number CTLIMM.015A, entitled "ANTI-NEOVASCULATURE PREPARATIONS FOR CANCER, filed on date even with this application (March 7, 2002). A tumor cell line is disclosed in Provisional U.S. Application No. 60/363,131, filed on March 7, 2002, attorney docket number CTLIMM.028PR, entitled "HLA-TRANSGENIC MURINE TUMOR CELL LINE."

Carcinoembryonic antigen (CEA) is a paradigmatic oncofetal protein first described in 1965 (Gold and Freedman, J. Exp. Med. 121: 439-462, 1965. Fuller references can be found in the Online Medelian Inheritance in Man; record *114890). It has officially been renamed carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5). Its expression is most strongly associated with adenocarcinomas of the epithelial lining of the digestive tract and in fetal colon. CEA is a member of the immunoglobulin supergene family and the defining member of the CEA subfamily.

Survivin, also known as Baculoviral IAP Repeat-Containing Protein 5 (BIRC5), is another protein with an oncofetal pattern of expression. It is a member of the inhibitor of apoptosis protein (IAP) gene family. It is widely overexpressed in cancers (Ambrosini, G. et al., *Nat. Med.* 3:917-921, 1997; Velculiscu V.E. et al., *Nat. Genet.* 23:387-388, 1999) and it's function as an inhibitor of apoptosis is believed to contribute to the malignant phenotype.

HER2/NEU is an oncogene related to the epidermal growth factor receptor (van de Vijver, et al., *New Eng. J. Med.* 319:1239-1245, 1988), and apparently identical to the c-ERBB2 oncogene (Di Fiore, et al., Science 237: 178-182, 1987). The over-expression of ERBB2 has been implicated in the neoplastic transformation of prostate cancer. As HER2 it is amplified and over-expressed in 25-30% of breast cancers among other tumors where expression level is correlated with the aggressiveness of the tumor (Slamon, et al., *New Eng. J. Med.* 344:783-792, 2001). A more detailed description is available in the Online Medelian Inheritance in Man; record *164870.

Useful epitopes were identified and tested as described in the following examples. However, these examples are intended for illustration purposes only, and should not be construed as limiting the scope of the invention in any way.

EXAMPLES

Example 1

Manufacture of epitopes.

A. Synthetic production of epitopes

Peptides having an amino acid sequence of any of SEQ ID NO: 1, 8, 9, 11-23, 26-29, 32-44, 47-54, 56-63, 66-68, or 108-602 are synthesized using either FMOC or tBOC solid phase synthesis methodologies. After synthesis, the peptides are cleaved from their supports with either trifluoroacetic acid or hydrogen fluoride, respectively, in the presence of appropriate protective scavengers. After removing the acid by evaporation, the peptides are extracted with ether to remove the scavengers and the crude, precipitated peptide is then lyophilized. Purity of the crude peptides is determined by HPLC, sequence analysis, amino acid analysis, counterion content analysis and other suitable means. If the crude peptides are pure enough (greater than or equal to about 90% pure), they can be used as is. If purification is required to meet drug substance specifications, the peptides are purified using one or a combination of the following: re-precipitation; reverse-phase, ion exchange, size exclusion or hydrophobic interaction chromatography; or counter-current distribution.

Drug product formulation

GMP-grade peptides are formulated in a parenterally acceptable aqueous, organic, or aqueous-organic buffer or solvent system in which they remain both physically and chemically stable and biologically potent. Generally, buffers or combinations of buffers or combinations of buffers and organic solvents are appropriate. The pH range is typically between 6 and 9. Organic modifiers or other excipients can be added to help solubilize and stabilize the peptides. These include detergents, lipids, co-solvents, antioxidants, chelators and reducing agents. In the case of a lyophilized product, sucrose or mannitol or other lyophilization aids can be added. Peptide solutions are sterilized by membrane filtration into their final container-closure system and either lyophilized for dissolution in the clinic, or stored until use.

B. Construction of expression vectors for use as nucleic acid vaccines

The construction of three generic epitope expression vectors is presented below. The particular advantages of these designs are set forth in PCT Publication No. WO 01/82963 and U.S. Patent Application No. 09/561,572 entitled "EXPRESSION VECTORS ENCODING EPITOPES OF TARGET-ASSOCIATED ANTIGENS." Additional vectors strategies for their design are disclosed in PCT Publication WO 03/063770; U.S. Patent Application No. 10/292,413, filed on November 7, 2002; and Provisional U.S. Patent application No. 60/336,968 entitled

"EXPRESSION VECTORS ENCODING EPITOPES OF TARGET-ASSOCIATED ANTIGENS AND METHODS FOR THEIR DESIGN," filed on November 7, 2001. The teachings and embodiments disclosed in said PCT publications and applications are contemplated as supporting principals and embodiments related to and useful in connection with the present invention.

A suitable *E. coli* strain was then transfected with the plasmid and plated out onto a selective medium. Several colonies were grown up in suspension culture and positive clones were identified by restriction mapping. The positive clone was then grown up and aliquotted into storage vials and stored at -70°C.

A mini-prep (QIAprep Spin Mini-prep: Qiagen, Valencia, CA) of the plasmid was then made from a sample of these cells and automated fluorescent dideoxy sequence analysis was used to confirm that the construct had the desired sequence.

<u>B.1 Construction of pVAX-EP1-IRES-EP2</u>

Overview:

The starting plasmid for this construct is pVAX1 purchased from Invitrogen (Carlsbad, CA). Epitopes EP1 and EP2 were synthesized by GIBCO BRL (Rockville, MD). The IRES was excised from pIRES purchased from Clontech (Palo Alto, CA).

Procedure:

1. pIRES was digested with EcoRI and NotI. The digested fragments were separated by agarose gel electrophoresis, and the IRES fragment was purified from the excised band.
2. pVAX1 was digested with EcoRI and NotI, and the pVAX1 fragment was gel-purified.
3. The purified pVAX1 and IRES fragments were then ligated together.
4. Competent E. coli of strain DH5α were transformed with the ligation mixture.
5. Minipreps were made from 4 of the resultant colonies.
6. Restriction enzyme digestion analysis was performed on the miniprep DNA. One recombinant colony having the IRES insert was used for further insertion of EP1 and EP2. This intermediate construct was called pVAX-IRES.
7. Oligonucleotides encoding EP1 and EP2 were synthesized.
8. EP1 was subcloned into pVAX-IRES between AflII and EcoRI sites, to make pVAX-EP1-IRES;
9. EP2 was subcloned into pVAX-EP1-IRES between SalI and NotI sites, to make the final construct pVAX-EP1-IRES-EP2.
10. The sequence of the EP1-IRES-EP2 insert was confirmed by DNA sequencing.

B 2. Construction of pVAX-EP1-IRES-EP2-ISS-NIS

Overview:

The starting plasmid for this construct was pVAX-EP1-IRES-EP2 (Example 1). The ISS (immunostimulatory sequence) introduced into this construct is AACGTT, and the NIS (standing for nuclear import sequence) used is the SV40 72bp repeat sequence. ISS-NIS was synthesized by GIBCO BRL. See Figure 2.

Procedure:

1. pVAX-EP1-IRES-EP2 was digested with NruI; the linearized plasmid was gel-purified.
2. ISS-NIS oligonucleotide was synthesized.
3. The purified linearized pVAX-EP1-IRES-EP2 and synthesized ISS-NIS were ligated together.
4. Competent E. coli of strain DH5α were transformed with the ligation product.
5. Minipreps were made from resultant colonies.
6. Restriction enzyme digestions of the minipreps were carried out.
7. The plasmid with the insert was sequenced.

B3. Construction of pVAX-EP2-UB-EP1

Overview:

The starting plasmid for this construct was pVAX1 (Invitrogen). EP2 and EP1 were synthesized by GIBCO BRL. Wild type Ubiquitin cDNA encoding the 76 amino acids in the construct was cloned from yeast.

Procedure:

1. RT-PCR was performed using yeast mRNA. Primers were designed to amplify the complete coding sequence of yeast Ubiquitin.
2. The RT-PCR products were analyzed using agarose gel electrophoresis. A band with the predicted size was gel-purified.
3. The purified DNA band was subcloned into pZERO1 at EcoRV site. The resulting clone was named pZERO-UB.
4. Several clones of pZERO-UB were sequenced to confirm the Ubiquitin sequence before further manipulations.
5. EP1 and EP2 were synthesized.
6. EP2, Ubiquitin and EP1 were ligated and the insert cloned into pVAX1 between BamHI and EcoRI, putting it under control of the CMV promoter.
7. The sequence of the insert EP2-UB-EP1 was confirmed by DNA sequencing.

Example 2

Identification of useful epitope variants.

The 10-mer FLPWHRLFLL (SEQ ID NO. 1) is identified as a useful epitope. Based on this sequence, numerous variants are made. Variants exhibiting activity in HLA binding assays (see Example 3, section 6) are identified as useful, and are subsequently incorporated into vaccines. Variants that increase the stability of binding, assayed can be particularly usefule, for example as described in WO 97/41440 entitled "Methods for Selecting and Producing T Cell Peptide Epitopes and Vaccines Incorporating Said Selected Epitopes." The teachings and embodiments disclosed in said PCT publication are contemplated as supporting principals and embodiments related to and useful in connection with the present invention.

The HLA-A2 binding of length variants of FLPWHRLFLL have been evaluated. Proteasomal digestion analysis indicates that the C-terminus of the 9-mer FLPWHRLFL (SEQ ID NO. 8) is also produced. Additionally the 9-mer LPWHRLFLL (SEQ ID NO. 9) can result from N-terminal trimming of the 10-mer. Both are predicted to bind to the HLA-A*0201 molecule, however of these two 9-mers, FLPWHRLFL displayed more significant binding and is preferred (see Figs. 3A and B).

In vitro proteasome digestion and N-terminal pool sequencing indicates that $\text{tyrosinase}_{207\text{-}216}$ (SEQ ID NO. 1) is produced more commonly than $\text{tyrosinase}_{207\text{-}215}$ (SEQ ID NO. 8), however the latter peptide displays superior immunogenicity, a potential concern in arriving at an optimal vaccine design. FLPWHRLFL, $\text{tyrosinase}_{207\text{-}215}$ (SEQ ID NO. 8) was used in an in vitro immunization of HLA-A2^{+} blood to generate CTL (see CTL Induction Cultures below). Using peptide pulsed T2 cells as targets in a standard chromium release assay it was found that the CTL induced by $\text{tyrosinase}_{207\text{-}215}$ (SEQ ID NO. 8) recognize $\text{tyrosinase}_{207\text{-}216}$ (SEQ ID NO. 1) targets equally well (see fig. 3C). These CTL also recognize the HLA-A2^{+}, tyrosinase^{+} tumor cell lines 624.38 and HTB64, but not 624.28 an HLA-A2^{-} derivative of 624.38 (fig. 3C). Thus the relative amounts of these two epitopes produced in vivo, does not become a concern in vaccine design.

CTL induction cultures

PBMCs from normal donors were purified by centrifugation in Ficoll-Hypaque from buffy coats. All cultures were carried out using the autologous plasma (AP) to avoid exposure to potential xenogeneic pathogens and recognition of FBS peptides. To favor the in vitro generation of peptide-specific CTL, we employed autologous dendritic cells (DC) as APCs. DC were generated and CTL were induced with DC and peptide from PBMCs as described (Keogh et al., 2001). Briefly, monocyte-enriched cell fractions were cultured for 5 days with GM-CSF and IL-4 and were cultured for 2 additional days in culture media with 2 μg/ml CD40 ligand to induce maturation. 2 x10^{6} CD8+-enriched T lymphocytes/well and 2 x10^{5} peptide-pulsed DC/well were co-cultured in 24-well plates in 2 ml RPMI supplemented with 10% AP, 10 ng/ml IL-7 and 20

IU/ml IL-2. Cultures were restimulated on days 7 and 14 with autologous irradiated peptide-pulsed DC.

Sequence variants of FLPWHRLFL are constructed as follow. Consistent with the binding coefficient table (see Table 3) from the NIH/BIMAS MHC binding prediction program (see reference in example 3 below), binding can be improved by changing the L at position 9, an anchor position, to V. Binding can also be altered, though generally to a lesser extent, by changes at non-anchor positions. Referring generally to Table 3, binding can be increased by employing residues with relatively larger coefficients. Changes in sequence can also alter immunogenicity independently of their effect on binding to MHC. Thus binding and/or immunogenicity can be improved as follows:

By substituting F,L,M,W, or Y for P at position 3; these are all bulkier residues that can also improve immunogenicity independent of the effect on binding. The amine and hydroxyl-bearing residues, Q and N; and S and T; respectively, can also provoke a stronger, cross-reactive response.

By substituting D or E for W at position 4 to improve binding; this addition of a negative charge can also make the epitope more immunogenic, while in some cases reducing cross-reactivity with the natural epitope. Alternatively the conservative substitutions of F or Y can provoke a cross-reactive response.

By substituting F for H at position 5 to improve binding. H can be viewed as partially charged, thus in some cases the loss of charge can hinder cross-reactivity. Substitution of the fully charged residues R or K at this position can enhance immunogenicity without disrupting charge-dependent cross-reactivity.

By substituting I, L, M, V, F, W, or Y for R at position 6. The same caveats and alternatives apply here as at position 5.

By substituting W or F for L at position 7 to improve binding. Substitution of V, I, S, T, Q, or N at this position are not generally predicted to reduce binding affinity by this model (the NIH algorithm), yet can be advantageous as discussed above.

Y and W, which are equally preferred as the Fs at positions 1 and 8, can provoke a useful cross-reactivity. Finally, while substitutions in the direction of bulkiness are generally favored to improve immunogenicity, the substitution of smaller residues such as A, S, and C, at positions 3-7 can be useful according to the theory that contrast in size, rather than bulkiness per se, is an important factor in immunogenicity. The reactivity of the thiol group in C can introduce other properties as discussed in Chen, J.-L., et al. *J. Immunol.* 165:948-955, 2000.

Table 3. 9-mer Coefficient Table for HLA-A*0201*

HLA Coefficient table for file "A_0201_standard"									
Amino Acid Type	1st	2nd	3rd	4th	5th	6th	7th	8th	9th
A	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
C	1.000	0.470	1.000	1.000	1.000	1.000	1.000	1.000	1.000
D	0.075	0.100	0.400	4.100	1.000	1.000	0.490	1.000	0.003
E	0.075	1.400	0.064	4.100	1.000	1.000	0.490	1.000	0.003
F	4.600	0.050	3.700	1.000	3.800	1.900	5.800	5.500	0.015
G	1.000	0.470	1.000	1.000	1.000	1.000	0.130	1.000	0.015
H	0.034	0.050	1.000	1.000	1.000	1.000	1.000	1.000	0.015
I	1.700	9.900	1.000	1.000	1.000	2.300	1.000	0.410	2.100
K	3.500	0.100	0.035	1.000	1.000	1.000	1.000	1.000	0.003
L	1.700	72.000	3.700	1.000	1.000	2.300	1.000	1.000	4.300
M	1.700	52.000	3.700	1.000	1.000	2.300	1.000	1.000	1.000
N	1.000	0.470	1.000	1.000	1.000	1.000	1.000	1.000	0.015
P	0.022	0.470	1.000	1.000	1.000	1.000	1.000	1.000	0.003
Q	1.000	7.300	1.000	1.000	1.000	1.000	1.000	1.000	0.003
R	1.000	0.010	0.076	1.000	1.000	1.000	0.200	1.000	0.003
S	1.000	0.470	1.000	1.000	1.000	1.000	1.000	1.000	0.015
T	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.500
V	1.700	6.300	1.000	1.000	1.000	2.300	1.000	0.410	14.000
W	4.600	0.010	8.300	1.000	1.000	1.700	7.500	5.500	0.015
Y	4.600	0.010	3.200	1.000	1.000	1.500	1.000	5.500	0.015

*This table and other comparable data that are publicly available are useful in designing epitope variants and in determining whether a particular variant is substantially similar, or is functionally similar.

Example 3

Cluster Analysis (SSX-2_{31-68}).

1. Epitope cluster region prediction:

The computer algorithms: SYFPEITHI (internet http:// access at syfpeithi.bmi-heidelberg.com/Scripts/MHCServer.dll/EpPredict.htm), based on the book "MHC Ligands and Peptide Motifs" by H.G.Rammensee, J.Bachmann and S.Stevanovic; and HLA Peptide Binding Predictions (NIH) (internet http:// access at bimas.dcrt.nih.gov/molbio/hla_bin), described in Parker, K. C., et al., *J. Immunol.* 152:163, 1994; were used to analyze the protein sequence of SSX-2 (GI:10337583). Epitope clusters (regions with higher than average density of peptide fragments with high predicted MHC affinity) were defined as described fully in U.S. Patent Application No. 09/561,571 entitled "EPITOPE CLUSTERS," filed on April 28, 2000. Using a epitope density ratio cutoff of 2, five and two clusters were defined using the SYFPETHI and NIH algorithms, respectively, and peptides score cutoffs of 16 (SYFPETHI) and 5 (NIH). The highest scoring peptide with the NIH algorithm, SSX-2_{41-49}, with an estimated halftime of dissociation of

>1000 min., does not overlap any other predicted epitope but does cluster with SSX-2_{57-65} in the NIH analysis.

2. Peptide synthesis and characterization:

SSX-2_{31-68}, YFSKEEWEKMKASEKIFYVYMKRKYEAMTKLGFKATLP (SEQ ID NO. 10) was synthesized by MPS (Multiple Peptide Systems, San Diego, CA 92121) using standard solid phase chemistry. According to the provided 'Certificate of Analysis', the purity of this peptide was 95%.

3. Proteasome digestion:

Proteasome was isolated from human red blood cells using the proteasome isolation protocol described in PCT Publication No. WO 01/82963 and U.S. Patent Application No. 09/561,074 entitled "METHOD OF EPITOPE DISCOVERY," filed on April 28, 2000. The teachings and embodiments disclosed in said PCT publication and application are contemplated as supporting principals and embodiments related to and useful in connection with the present invention. SDS-PAGE, western-blotting, and ELISA were used as quality control assays. The final concentration of proteasome was 4 mg/ml, which was determined by non-interfering protein assay (Geno Technologies Inc.). Proteasomes were stored at -70°C in 25 μl aliquots.

SSX-2_{31-68} was dissolved in Milli-Q water, and a 2 mM stock solution prepared and 20μL aliquots stored at -20°C.

1 tube of proteasome (25 μL) was removed from storage at-70°C and thawed on ice. It was then mixed thoroughly with 12.5μL of 2mM peptide by repipetting (samples were kept on ice). A 5μL sample was immediately removed after mixing and transferred to a tube containing 1.25μL 10%TFA (final concentration of TFA was 2%); the T=0 min sample. The proteasome digestion reaction was then started and carried out at 37°C in a programmable thermal controller. Additional 5μL samples were taken out at 15, 30, 60, 120, 180 and 240 min respectively, the reaction was stopped by adding the sample to 1.25μL 10% TFA as before. Samples were kept on ice or frozen until being analyzed by MALDI-MS. All samples were saved and stored at –20°C for HPLC analysis and N-terminal sequencing. Peptide alone (without proteasome) was used as a blank control: 2 μL peptide + 4μL Tris buffer (20 mM, pH 7.6) + 1.5μL TFA.

4. MALDI-TOF MS measurements:

For each time point 0.3 μL of matrix solution (10mg/ml α-cyano-4-hydroxycinnamic acid in AcCN/H_2O (70:30)) was first applied on a sample slide, and then an equal volume of digested sample was mixed gently with matrix solution on the slide. The slide was allowed to dry at ambient air for 3-5 min. before acquiring the mass spectra. MS was performed on a Lasermat 2000 MALDI-TOF mass spectrometer that was calibrated with peptide/protein standards. To improve the accuracy of measurement, the molecular ion weight (MH^+) of the peptide substrate was used as

an internal calibration standard. The mass spectrum of the T=120 min. digested sample is shown in figure 4.

5. MS data analysis and epitope identification:

To assign the measured mass peaks, the computer program MS-Product, a tool from the UCSF Mass Spectrometry Facility (http:// accessible at prospector.ucsf.edu/ucsfhtml3.4/msprod.htm), was used to generate all possible fragments (N- and C-terminal ions, and internal fragments) and their corresponding molecular weights. Due to the sensitivity of the mass spectrometer, average molecular weight was used. The mass peaks observed over the course of the digestion were identified as summarized in Table 4.

Fragments co-C-terminal with 8-10 amino acid long sequences predicted to bind HLA by the SYFPEITHI or NIH algorithms were chosen for further study. The digestion and prediction steps of the procedure can be usefully practiced in any order. Although the substrate peptide used in proteasomal digest described here was specifically designed to include predicted HLA-A2.1 binding sequences, the actual products of digestion can be checked after the fact for actual or predicted binding to other MHC molecules. Selected results are shown in Table 5.

Table 4. SSX-2_{31-68} Mass Peak Identification.

MS PEAK (measured)	PEPTIDE	SEQUENCE	CALCULATED MASS (MH^+)
988.23	31-37	YFSKEEW	989.08
1377.68±2.38	31-40	**YFSKEEWEKM**	1377.68
1662.45±1.30	31-43	YFSKEEWEKMKAS	1663.90
2181.72±0.85	31-47	YFSKEEWE**KMKASEKIF**	2181.52
2346.6	31-48	YFSKEEWE**KMKASEKIFY**	2344.71
1472.16±1.54	38-49	EKM**KASEKIFYV**	1473.77
2445.78±1.18	31-49*	YFSKEEWEKM**KASEKIFYV**	2443.84
2607.	31-50	YFSKEEWEKM**KASEKIFYVY**	2607.02
1563.3	50-61	YMK**RKYEAMTKL**	1562.93
3989.9	31-61	YFSKEEWEKMKASEKIFYVYMK**RKYEAMTKL**	3987.77
1603.74±1.53	51-63	MKR**KYEAMTKLGF**	1603.98
1766.45±1.5	50-63	YMKR**KYEAMTKLGF**	1767.16
1866.32±1.22	49-63	VYMKR**KYEAMTKLGF**	1866.29
4192.6	31-63	YFSKEEWEKMKASEKIFYVYMKR**KYEAMTKLGF**	4192.00
4392.1	31-65**	YFSKEEWEKMKASEKIFYVYMKRKYEAMTKLGFKA	4391.25

Boldface sequence correspond to peptides predicted to bind to MHC.

* On the basis of mass alone this peak could also have been assigned to the peptide 32-50, however proteasomal removal of just the N-terminal amino acid is unlikely. N-terminal sequencing (below) verifies the assignment to 31-49.

** On the basis of mass this fragment might also represent 33-68. N-terminal sequencing below is consistent with the assignment to 31-65.

Table 5. Predicted HLA binding by proteasomally generated fragments

SEQ ID NO.	PEPTIDE	HLA	SYFPEITHI	NIH
11	FSKEEWEKM	B*3501	NP†	90
12	KMKASEKIF	B*08	17	<5
13 & (14)	(K)MKASEKIFY	A1	19 (19)	<5
15 &(16)	(M)KASEKIFYV	A*0201	22 (16)	1017
		B*08	17	<5
		B*5101	22 (13)	60
		B*5102	NP	133
		B*5103	NP	121
17 & (18)	(K)ASEKIFYVY	A1	34 (19)	14
19 & (20)	(K)RKYEAMTKL	A*0201	15	<5
		A26	15	NP
		B14	NP	45 (60)
		B*2705	21	15
		B*2709	16	NP
		B*5101	15	<5
21	KYEAMTKLGF	A1	16	<5
		A24	NP	300
22	YEAMTKLGF	B*4403	NP	80
23	EAMTKLGF	B*08	22	<5

†No prediction

As seen in Table 5, N-terminal addition of authentic sequence to epitopes can generate epitopes for the same or different MHC restriction elements. Note in particular the pairing of (K)RKYEAMTKL (SEQ ID NOS 19 and (20)) with HLA-B14, where the 10-mer has a longer predicted halftime of dissociation than the co-C-terminal 9-mer. Also note the case of the 10-mer KYEAMTKLGF (SEQ ID NO. 21) which can be used as a vaccine useful with several MHC types by relying on N-terminal trimming to create the epitopes for HLA-B*4403 and –B*08.

6. HLA-A0201 binding assay:

Binding of the candidate epitope KASEKIFYV, SSX-2_{41-49}, (SEQ ID NO. 15) to HLA-A2.1 was assayed using a modification of the method of Stauss et al., (Proc Natl Acad Sci USA 89(17):7871-5 (1992)). Specifically, T2 cells, which express empty or unstable MHC molecules on their surface, were washed twice with Iscove's modified Dulbecco's medium (IMDM) and cultured overnight in serum-free AIM-V medium (Life Technologies, Inc., Rockville, MD) supplemented with human ß2-microglobulin at 3μg/ml (Sigma, St. Louis, MO) and added peptide, at 800, 400, 200, 100, 50, 25, 12.5, and 6.25 μg/ml.in a 96-well flat-bottom plate at $3x10^5$ cells/200 μl (microliter)/well. Peptide was mixed with the cells by repipeting before distributing to the plate (alternatively peptide can be added to individual wells), and the plate was rocked gently for 2 minutes. Incubation was in a 5% CO_2 incubator at 37°C. The next day the unbound peptide was removed by washing twice with serum free RPMI medium and a saturating amount of anti-class I HLA monoclonal antibody, fluorescein isothiocyanate (FITC)-conjugated anti-HLA A2, A28 (One

Lambda, Canoga Park, CA) was added. After incubation for 30 minutes at 4°C, cells were washed 3 times with PBS supplemented with 0.5% BSA, 0.05%(w/v) sodium azide, pH 7.4-7.6 (staining buffer). (Alternatively W6/32 (Sigma) can be used as the anti-class I HLA monoclonal antibody the cells washed with staining buffer and then incubated with fluorescein isothiocyanate (FITC)-conjugated goat F(ab') antimouse-IgG (Sigma) for 30 min at 4°C and washed 3 times as before.) The cells were resuspended in 0.5 ml staining buffer. The analysis of surface HLA-A2.1 molecules stabilized by peptide binding was performed by flow cytometry using a FACScan (Becton Dickinson, San Jose, CA). If flow cytometry is not to be performed immediately the cells can be fixed by adding a quarter volume of 2% paraformaldehyde and storing in the dark at 4°C.

The results of the experiment are shown in Figure 5. SSX-2_{41-49} (SEQ ID NO. 15) was found to bind HLA-A2.1 to a similar extent as the known A2.1 binder FLPSDYFPSV (HBV_{18-27}; SEQ ID NO: 24) used as a positive control. An HLA-B44 binding peptide, AEMGKYSFY (SEQ ID NO: 25), was used as a negative control. The fluoresence obtained from the negative control was similar to the signal obtained when no peptide was used in the assay. Positive and negative control peptides were chosen from Table 18.3.1 in *Current Protocols in Immunology* p. 18.3.2, John Wiley and Sons, New York, 1998.

7. Immunogenicity:

A. *In vivo* immunization of mice.

HHD1 transgenic A*0201 mice (Pascolo, S., et al. *J. Exp. Med.* 185:2043-2051, 1997) were anesthetized and injected subcutaneously at the base of the tail, avoiding lateral tail veins, using 100 μl containing 100 nmol of SSX-2_{41-49} (SEQ ID NO. 15) and 20 μg of HTL epitope peptide in PBS emulsified with 50 μl of IFA (incomplete Freund's adjuvant).

B. Preparation of stimulating cells (LPS blasts).

Using spleens from 2 naive mice for each group of immunized mice, un-immunized mice were sacrificed and the carcasses were placed in alcohol. Using sterile instruments, the top dermal layer of skin on the mouse's left side (lower mid-section) was cut through, exposing the peritoneum. The peritoneum was saturated with alcohol, and the spleen was aseptically extracted. The spleen was placed in a petri dish with serum-free media. Splenocytes were isolated by using sterile plungers from 3 ml syringes to mash the spleens. Cells were collected in a 50 ml conical tubes in serum-free media, rinsing dish well. Cells were centrifuged (12000 rpm, 7 min) and washed one time with RPMI. Fresh spleen cells were resuspended to a concentration of $1x10^6$ cells per ml in RPMI-10%FCS (fetal calf serum). 25g/ml lipopolysaccharide and 7 μg/ml Dextran Sulfate were added. Cell were incubated for 3 days in T-75 flasks at 37°C, with 5% CO_2. Splenic blasts were collected in 50 ml tubes pelleted (12000 rpm, 7 min) and resuspended to $3X10^7$/ml in RPMI. The blasts were pulsed with the priming peptide at 50 μg/ml, RT 4hr. mitomycin C-treated at 25μg/ml, 37^0C, 20 min and washed three times with DMEM.

C. *In vitro* stimulation.

3 days after LPS stimulation of the blast cells and the same day as peptide loading, the primed mice were sacrificed (at 14 days post immunization) to remove spleens as above. $3x10^6$ splenocytes were co-cultured with $1x10^6$ LPS blasts/well in 24-well plates at 37°C, with 5% CO_2 in DMEM media supplemented with 10% FCS, $5x10^{-5}$ M β-mercaptoethanol, 100μg/ml streptomycin and 100 IU/ml penicillin. Cultures were fed 5% (vol/vol) ConA supernatant on day 3 and assayed for cytolytic activity on day 7 in a ^{51}Cr-release assay.

D. Chromium-release assay measuring CTL activity.

To assess peptide specific lysis, $2x10^6$ T2 cells were incubated with 100 μCi sodium chromate together with 50 μg/ml peptide at 37°C for 1 hour. During incubation they were gently shaken every 15 minutes. After labeling and loading, cells were washed three times with 10 ml of DMEM-10% FCS, wiping each tube with a fresh Kimwipe after pouring off the supernatant. Target cells were resuspended in DMEM-10% FBS $1x10^5$/ml. Effector cells were adjusted to $1x10^7$/ml in DMEM-10% FCS and 100 μl serial 3-fold dilutions of effectors were prepared in U-bottom 96-well plates. 100 μl of target cells were added per well. In order to determine spontaneous release and maximum release, six additional wells containing 100 μl of target cells were prepared for each target. Spontaneous release was revealed by incubating the target cells with 100 μl medium; maximum release was revealed by incubating the target cells with 100μl of 2% SDS. Plates were then centrifuged for 5 min at 600 rpm and incubated for 4 hours at 37°C in 5% CO_2 and 80% humidity. After the incubation, plates were then centrifuged for 5 min at 1200 rpm. Supernatants were harvested and counted using a gamma counter. Specific lysis was determined as follows: % specific release = [(experimental release - spontaneous release)/(maximum release - spontaneous release)] x 100.

Results of the chromium release assay demonstrating specific lysis of peptide pulsed target cells are shown in figure 6.

8. Cross-reactivity with other SSX proteins:

SSX-2_{41-49} (SEQ ID NO. 15) shares a high degree of sequence identity with the same region of the other SSX proteins. The surrounding regions have also been generally well conserved. Thus the housekeeping proteasome can cleave following V_{49} in all five sequences. Moreover, SSX_{41-49} is predicted to bind HLA-A*0201 (see Table 6). CTL generated by immunization with SSX-2_{41-49} cross-react with tumor cells expressing other SSX proteins.

Table 6. SSX_{41-49} – A*0201 Predicted Binding

SEQ ID NO.	Family Member	Sequence	SYFPEITHI Score	NIH Score
15	SSX-2	KASEKIFYV	22	1017
26	SSX-1	KYSEKISYV	18	1.7
27	SSX-3	KVSEKIVYV	24	1105
28	SSX-4	KSSEKIVYV	20	82
29	SSX-5	KASEKIIYV	22	175

Example 4

Cluster Analysis ($PSMA_{163-192}$).

[0227] A peptide, AFSPQGMPEGDLVYVNYARTEDFFKLERDM, $PSMA_{163-192}$, (SEQ ID NO. 30), containing an A1 epitope cluster from prostate specific membrane antigen, $PSMA_{168-190}$ (SEQ ID NO. 31) was synthesized using standard solid-phase F-moc chemistry on a 433A ABI Peptide synthesizer. After side chain deprotection and cleavage from the resin, peptide first dissolved in formic acid and then diluted into 30% Acetic acid, was run on a reverse-phase preparative HPLC C4 column at following conditions: linear AB gradient (5% B/min) at a flow rate of 4 ml/min, where eluent A is 0.1% aqueous TFA and eluent B is 0.1% TFA in acetonitrile. A fraction at time 16.642 min containing the expected peptide, as judged by mass spectrometry, was pooled and lyophilized. The peptide was then subjected to proteasome digestion and mass spectrum analysis essentially as described above. Prominent peaks from the mass spectra are summarized in Table 7.

Table 7. $PSMA_{163-192}$ Mass Peak Identification.

PEPTIDE	SEQUENCE	CALCULATED MASS (MH^+)
163-177	AFSPQG**MPEGDLVYV**	1610.0
178-189	NYA**RTEDFFKLE**	1533.68
170-189	PEGDLVYVNYA**RTEDFFKLE**	2406.66
178-191	NYARTEDFFKLERD	1804.95
170-191	PEGDLVYVNYARTEDFFKLERD	2677.93
178-192	NYARTEDFFKLERDM	1936.17
163-176	AFSPQ**GMPEGDLVY**	1511.70
177-192	VNYARTEDFFKLERDM	2035.30
163-179	AFSPQGMP**EGDLVYVNY**	1888.12
180-192	ARTEDFFKLERDM	1658.89
163-183	AFSPQGMPEGD**LVYVNYARTE**	2345.61
184-192	DFFKLERDM	1201.40
176-192	YVNYARTEDFFKLERDM	2198.48
167-185	QGMPEGDLVY**VNYARTEDF**	2205.41
178-186	**NYARTEDFF**	1163.22

Boldface sequences correspond to peptides predicted to bind to MHC, see Table 8.

N-terminal Pool Sequence Analysis

One aliquot at one hour of the proteasomal digestion (see Example 3 part 3 above) was subjected to N-terminal amino acid sequence analysis by an ABI 473A Protein Sequencer (Applied Biosystems, Foster City, CA). Determination of the sites and efficiencies of cleavage was based on consideration of the sequence cycle, the repetitive yield of the protein sequencer, and the relative yields of amino acids unique in the analyzed sequence. That is if the unique (in the analyzed sequence) residue X appears only in the nth cycle a cleavage site exists n-1 residues before it in the N-terminal direction. In addition to helping resolve any ambiguity in the assignment of mass to sequences, these data also provide a more reliable indication of the relative yield of the various fragments than does mass spectrometry.

For $PSMA_{163-192}$ (SEQ ID NO. 30) this pool sequencing supports a single major cleavage site after V_{177} and several minor cleavage sites, particularly one after Y_{179}. Reviewing the results presented in figures 7A-C reveals the following:

S at the 3rd cycle indicating presence of the N-terminus of the substrate.

Q at the 5th cycle indicating presence of the N-terminus of the substrate.

N at the 1st cycle indicating cleavage after V_{177}.

N at the 3rd cycle indicating cleavage after V_{175}. Note the fragment 176-192 in Table 7.

T at the 5th cycle indicating cleavage after V_{177}.

T at the 1st –3rd cycles, indicating increasingly common cleavages after R_{181}, A_{180} and Y_{179}. Only the last of these correspond to peaks detected by mass spectrometry; 163-179 and 180-192, see Table 7. The absence of the others can indicate that they are on fragments smaller than were examined in the mass spectrum.

K at the 4th, 8th, and 10th cycles indicating cleavages after E_{183}, Y_{179}, and V_{177}, respectively, all of which correspond to fragments observed by mass spectroscopy. See Table 7.

A at the 1st and 3rd cycles indicating presence of the N-terminus of the substrate and cleavage after V_{177}, respectively.

P at the 4th and 8th cycles indicating presence of the N-terminus of the substrate.

G at the 6th and 10th cycles indicating presence of the N-terminus of the substrate.

M at the 7th cycle indicating presence of the N-terminus of the substrate and/or cleavage after F_{185}.

M at the 15th cycle indicating cleavage after V_{177}.

The 1st cycle can indicate cleavage after D_{191}, see Table 7.

R at the 4th and 13th cycle indicating cleavage after V_{177}.

R at the 2nd and 11th cycle indicating cleavage after Y_{179}.

V at the 2nd, 6th, and 13th cycle indicating cleavage after V_{175}, M_{169} and presence of the N-terminus of the substrate, respectively. Note fragments beginning at 176 and 170 in Table 7.

Y at the 1st, 2nd, and 14th cycles indicating cleavage after V_{175}, V_{177}, and presence of the N-terminus of the substrate, respectively.

L at the11th and 12th cycles indicating cleavage after V_{177}, and presence of the N-terminus of the substrate, respectively, is the interpretation most consistent with the other data. Comparing to the mass spectrometry results we see that L at the 2nd, 5th, and 9th cycles is consistent with cleavage after F_{186}, E_{183} or M_{169}, and Y_{179}, respectively. See Table 7.

Epitope Identification

Fragments co-C-terminal with 8-10 amino acid long sequences predicted to bind HLA by the SYFPEITHI or NIH algorithms were chosen for further analysis. The digestion and prediction steps of the procedure can be usefully practiced in any order. Although the substrate peptide used in proteasomal digest described here was specifically designed to include a predicted HLA-A1 binding sequence, the actual products of digestion can be checked after the fact for actual or predicted binding to other MHC molecules. Selected results are shown in Table 8.

Table 8. Predicted HLA binding by proteasomally generated fragments

SEQ ID NO	PEPTIDE	HLA	SYFPEITHI	NIH
32 & (33)	(G) MPEGDLVYV	A*0201	17 (27)	(2605)
		B*0702	20	<5
		B*5101	22	314
34 & (35)	(Q) GMPEGDLVY	A1	24 (26)	<5
		A3	16 (18)	36
		B*2705	17	25
36	MPEGDLVY	B*5101	15	NP†
37 & (38)	(P) EGDLVYVNY	A1	27 (15)	12
		A26	23 (17)	NP
39	LVYVNYARTE	A3	21	<5
40 & (41)	(Y) VNYARTEDF	A26	(20)	NP
		B*08	15	<5
		B*2705	12	50
42	NYARTEDFF	A24	NP†	100
		Cw*0401	NP	120
43	YARTEDFF	B*08	16	<5
44	RTEDFFKLE	A1	21	<5
		A26	15	NP

†No prediction

HLA-A*0201 binding assay:

HLA-A*0201 binding studies were preformed with $PSMA_{168-177}$, GMPEGDLVYV, (SEQ ID NO. 33) essentially as described in Example 3 above. As seen in figure 8, this epitope exhibits significant binding at even lower concentrations than the positive control peptides. The Melan-A peptide used as a control in this assay (and throughout this disclosure), ELAGIGILTV, is actually a variant of the natural sequence (EAAGIGILTV) and exhibits a high affinity in this assay.

Example 5

Cluster Analysis (PSMA$_{281-310}$).

Another peptide, RGIAEAVGLPSIPVHPIGYYDAQKLLEKMG, PSMA$_{281-310}$, (SEQ ID NO. 45), containing an A1 epitope cluster from prostate specific membrane antigen, PSMA$_{283-307}$ (SEQ ID NO. 46), was synthesized using standard solid-phase F-moc chemistry on a 433A ABI Peptide synthesizer. After side chain deprotection and cleavage from the resin, peptide in ddH2O was run on a reverse-phase preparative HPLC C18 column at following conditions: linear AB gradient (5% B/min) at a flow rate of 4 ml/min, where eluent A is 0.1% aqueous TFA and eluent B is 0.1% TFA in acetonitrile. A fraction at time 17.061 min containing the expected peptide as judged by mass spectrometry, was pooled and lyophilized. The peptide was then subjected to proteasome digestion and mass spectrum analysis essentially as described above. Prominent peaks from the mass spectra are summarized in Table 9.

Table 9. PSMA$_{281-310}$ Mass Peak Identification.

PEPTIDE	SEQUENCE	CALCULATED MASS (MH^+)
281-297	RGIAEAV**GLPSIPVHPI***	1727.07
286-297	AV**GLPSIPVHPI****	1200.46
287-297	V**GLPSIPVHPI**	1129.38
288-297	**GLPSIPVHPI**†	1030.25
298-310	GYYDAQKLLEKMG‡	1516.5
298-305	GYYDAQKL§	958.05
281-305	RGIAEAVGLPSIPVHP**IGYYDAQKL**	2666.12
281-307	RGIAEAVGLPSIPVHPIG**YYDAQKLLE**	2908.39
286-307	AVGLPSIPVHPIG**YYDAQKLLE**¶	2381.78
287-307	VGLPSIPVHPIG**YYDAQKLLE**	2310.70
288-307	GLPSIPVHPIG**YYDAQKLLE**#	2211.57
281-299	RGIAEAVGLP**SIPVHPIGY**	1947
286-299	AVGLP**SIPVHPIGY**	1420.69
287-299	VGLP**SIPVHPIGY**	1349.61
288-299	GLP**SIPVHPIGY**	1250.48
287-310	VGLPSIPVHPIGYYDAQKLLEKMG	2627.14
288-310	GLPSIPVHPIGYYDAQKLLEKMG	2528.01

Boldface sequences correspond to peptides predicted to bind to MHC, see Table 10.
*By mass alone this peak could also have been 296-310 or 288-303.
**By mass alone this peak could also have been 298-307. Combination of HPLC and mass spectrometry show that at some later time points this peak is a mixture of both species.
† By mass alone this peak could also have been 289-298.
? By mass alone this peak could also have been 281-295 or 294-306.
§ By mass alone this peak could also have been 297-303.
¶ By mass alone this peak could also have been 285-306.
# By mass alone this peak could also have been 288-303.

None of these alternate assignments are supported N-terminal pool sequence analysis.

N-terminal Pool Sequence Analysis

One aliquot at one hour of the proteasomal digestion (see Example 3 part 3 above) was subjected to N-terminal amino acid sequence analysis by an ABI 473A Protein Sequencer (Applied Biosystems, Foster City, CA). Determination of the sites and efficiencies of cleavage was based on consideration of the sequence cycle, the repetitive yield of the protein sequencer, and the relative yields of amino acids unique in the analyzed sequence. That is if the unique (in the analyzed sequence) residue X appears only in the nth cycle a cleavage site exists n-1 residues before it in the N-terminal direction. In addition to helping resolve any ambiguity in the assignment of mass to sequences, these data also provide a more reliable indication of the relative yield of the various fragments than does mass spectrometry.

For $PSMA_{\underline{281-310}}$ (SEQ ID NO. 45) this pool sequencing supports two major cleavage sites after V_{287} and I_{297} among other minor cleavage sites. Reviewing the results presented in Fig. 9 reveals the following:

S at the 4th and 11th cycles indicating cleavage after V_{287} and presence of the N-terminus of the substrate, respectively.

H at the 8th cycle indicating cleavage after V_{287}. The lack of decay in peak height at positions 9 and 10 versus the drop in height present going from 10 to 11 can suggest cleavage after A_{286} and E_{285} as well, rather than the peaks representing latency in the sequencing reaction.

D at the 2nd, 4th, and 7th cycles indicating cleavages after Y_{299}, I_{297}, and V_{294}, respectively. This last cleavage is not observed in any of the fragments in Table 10 or in the alternate assignments in the notes below.

Q at the 6th cycle indicating cleavage after I_{297}.

M at the 10th and 12th cycle indicating cleavages after Y_{299} and I_{297}, respectively.

Epitope Identification

Fragments co-C-terminal with 8-10 amino acid long sequences predicted to bind HLA by the SYFPEITHI or NIH algorithms were chosen for further study. The digestion and prediction steps of the procedure can be usefully practiced in any order. Although the substrate peptide used in proteasomal digest described here was specifically designed to include a predicted HLA-A1 binding sequence, the actual products of digestion can be checked after the fact for actual or predicted binding to other MHC molecules. Selected results are shown in Table 10.

Table 10.

Predicted HLA binding by proteasomally generated fragments: $PSMA_{281-310}$

SEQ ID NO.	PEPTIDE	HLA	SYFPEITHI	NIH
47 & (48)	(G)LPSIPVHPI	A*0201	16 (24)	(24)
		B*0702/B7	23	12
		B*5101	24	572
		Cw*0401	NP†	20
49 & (50)	(P)IGYYDAQKL	A*0201	(16)	<5
		A26	(20)	NP
		B*2705	16	25
		B*2709	15	NP
		B*5101	21	57
		Cw*0301	NP	24
51 & (52)	(P)SIPVHPIGY	A1	21 (27)	<5
		A26	22	NP
		A3	16	<5
53	IPVHPIGY	B*5101	16	NP
54	YYDAQKLLE	A1	22	<5

†No prediction

As seen in Table 10, N-terminal addition of authentic sequence to epitopes can often generate still useful, even better epitopes, for the same or different MHC restriction elements. Note for example the pairing of (G)LPSIPVHPI with HLA-A*0201, where the 10-mer can be used as a vaccine useful with several MHC types by relying on N-terminal trimming to create the epitopes for HLA-B7, -B*5101, and Cw*0401.

HLA-A*0201 binding assay:

HLA-A*0201 binding studies were preformed with $PSMA_{288-297}$, GLPSIPVHPI, (SEQ ID NO. 48) essentially as described in Examples 3 and 4 above. As seen in figure 8, this epitope exhibits significant binding at even lower concentrations than the positive control peptides.

Example 6

Cluster Analysis ($PSMA_{454-481}$).

Another peptide, SSIEGNYTLRVDCTPLMYSLVHLTKEL, $PSMA_{454-481}$, (SEQ ID NO. 55) containing an epitope cluster from prostate specific membrane antigen, was synthesized by MPS (purity >95%) and subjected to proteasome digestion and mass spectrum analysis as described above. Prominent peaks from the mass spectra are summarized in Table 11.

Table 11. $PSMA_{454-481}$ Mass Peak Identification.

MS PEAK (measured)	PEPTIDE	SEQUENCE	CALCULATED MASS (MH^+)
1238.5	454-464	SS**IEGNYTLRV**	1239.78

1768.38±0.60	454-469	SSIEGNY**TLRVDCTPL**	1768.99
1899.8	454-470	SSIEGNYT**LRVDCTPLM**	1900.19
1097.63±0.91	463-471	**RVDCTPLMY**	1098.32
2062.87±0.68	454-471*	SSIEGNYTL**RVDCTPLMY**	2063.36
1153	472-481**	SLVHNLTKEL	1154.36
1449.93±1.79	470-481	MYSLVHNLTKEL	1448.73

Boldface sequence correspond to peptides predicted to bind to MHC, see Table 12.

* On the basis of mass alone this peak could equally well be assigned to the peptide 455-472 however proteasomal removal of just the N-terminal amino acid is considered unlikely. If the issue were important it could be resolved by N-terminal sequencing.

**On the basis of mass this fragment might also represent 455-464.

Epitope Identification

Fragments co-C-terminal with 8-10 amino acid long sequences predicted to bind HLA by the SYFPEITHI or NIH algorithms were chosen for further study. The digestion and prediction steps of the procedure can be usefully practiced in any order. Although the substrate peptide used in proteasomal digest described here was specifically designed to include predicted HLA-A2.1 binding sequences, the actual products of digestion can be checked after the fact for actual or predicted binding to other MHC molecules. Selected results are shown in Table 12.

Table 12. Predicted HLA binding by proteasomally generated fragments

SEQ ID NO	PEPTIDE	HLA	SYFPEITHI	NIH
56 & (57)	(S)IEGNYTLRV	A1	(19)	<5
58	EGNYTLRV	A*0201	16 (22)	<5
		B*5101	15	NP†
59 & (60)	(Y)TLRVDCTPL	A*0201	20 (18)	(5)
		A26	16 (18)	NP
		B7	14	40
		B8	23	<5
		B*2705	12	30
		Cw*0301	NP	(30)
61	LRVDCTPLM	B*2705	20	600
		B*2709	20	NP
62 & (63)	(L)RVDCTPLMY	A1	32 (22)	125 (13.5)
		A3	25	<5
		A26	22	NP
		B*2702	NP	(200)
		B*2705	13 (NP)	(1000)

†No prediction

As seen in Table 12, N-terminal addition of authentic sequence to epitopes can often generate still useful, even better epitopes, for the same or different MHC restriction elements. Note for example the pairing of (L)RVDCTPLMY (SEQ ID NOS 62 and (63)) with HLA-B*2702/5, where the 10-mer has substantial predicted halftimes of dissociation and the co-C-

terminal 9-mer does not. Also note the case of SIEGNYTLRV (SEQ ID NO 57) a predicted HLA-A*0201 epitope which can be used as a vaccine useful with HLA-B*5101 by relying on N-terminal trimming to create the epitope.

HLA-A*0201 binding assay

HLA-A*0201 binding studies were preformed, essentially as described in Example 3 above, with $PSMA_{460-469}$, TLRVDCTPL, (SEQ ID NO. 60). As seen in figure 10, this epitope was found to bind HLA-A2.1 to a similar extent as the known A2.1 binder FLPSDYFPSV (HBV_{18-27}; SEQ ID NO: 24) used as a positive control. Additionally, $PSMA_{461-469}$, (SEQ ID NO. 59) binds nearly as well.

ELISPOT analysis: $PSMA_{463-471}$ (SEQ ID NO. 62)

The wells of a nitrocellulose-backed microtiter plate were coated with capture antibody by incubating overnight at 4°C using 50 μl (microliter)/well of 4μg/ml murine anti-human γ (gamma)-IFN monoclonal antibody in coating buffer (35 mM sodium bicarbonate, 15 mM sodium carbonate, pH 9.5). Unbound antibody was removed by washing 4 times 5 min. with PBS. Unbound sites on the membrane then were blocked by adding 200μl (microliter)/well of RPMI medium with 10% serum and incubating 1 hr. at room temperature. Antigen stimulated $CD8^+$ T cells, in 1:3 serial dilutions, were seeded into the wells of the microtiter plate using 100μl (microliter)/well, starting at $2x10^5$ cells/well. (Prior antigen stimulation was essentially as described in Scheibenbogen, C. et al. *Int. J. Cancer* 71:932-936, 1997. $PSMA_{462-471}$ (SEQ ID NO. 62) was added to a final concentration of 10μg/ml and IL-2 to 100 U/ml and the cells cultured at 37°C in a 5% CO_2, water-saturated atmosphere for 40 hrs. Following this incubation the plates were washed with 6 times 200 μl (microliter)/well of PBS containing 0.05% Tween-20 (PBS-Tween). Detection antibody, 50μl (microliter)/well of 2g/ml biotinylated murine anti-human γ (gamma)-IFN monoclonal antibody in PBS+10% fetal calf serum, was added and the plate incubated at room temperature for 2 hrs. Unbound detection antibody was removed by washing with 4 times 200 μl of PBS-Tween. 100μl of avidin-conjugated horseradish peroxidase (Pharmingen, San Diego, CA) was added to each well and incubated at room temperature for 1 hr. Unbound enzyme was removed by washing with 6 times 200 μl of PBS-Tween. Substrate was prepared by dissolving a 20 mg tablet of 3-amino 9-ethylcoarbasole in 2.5 ml of N, N-dimethylformamide and adding that solution to 47,5 ml of 0.05 M phosphate-citrate buffer (pH 5.0). 25 μl of 30% H_2O_2 was added to the substrate solution immediately before distributing substrate at100 μl (microliter)/well and incubating the plate at room temperature. After color development (generally 15-30 min.), the reaction was stopped by washing the plate with water. The plate was air dried and the spots counted using a stereomicroscope.

Figure 11 shows the detection of $PSMA_{463-471}$ (SEQ ID NO. 62)-reactive HLA-$A1^+$ $CD8^+$ T cells previously generated in cultures of HLA-$A1^+$ $CD8^+$ T cells with autologous dendritic cells

plus the peptide. No reactivity is detected from cultures without peptide (data not shown). In this case it can be seen that the peptide reactive T cells are present in the culture at a frequency between 1 in 2.2×10^4 and 1 in 6.7×10^4. That this is truly an HLA-A1-restricted response is demonstrated by the ability of anti-HLA-A1 monoclonal antibody to block γ (gamma) IFN production; see figure 12.

Example 7

Cluster Analysis (PSMA$_{653-687}$).

Another peptide, FDKSNPIVLRMMNDQLMFLERAFIDPLGLPDRP FY PSMA$_{653-687}$, (SEQ ID NO. 64) containing an A2 epitope cluster from prostate specific membrane antigen, PSMA$_{660-681}$ (SEQ ID NO 65), was synthesized by MPS (purity >95%) and subjected to proteasome digestion and mass spectrum analysis as described above. Prominent peaks from the mass spectra are summarized in Table 13.

Table 13. PSMA$_{653-687}$ Mass Peak Identification.

MS PEAK (measured)	PEPTIDE	SEQUENCE	CALCULATED MASS (MH$^+$)
906.17±0.65	681-687**	LPDRPFY	908.05
1287.73±0.76	677-687**	DPLGLPDRPFY	1290.47
1400.3±1.79	676-687	IDPLGLPDRPFY	1403.63
1548.0±1.37	675-687	FIDPLGLPDRPFY	1550.80
1619.5±1.51	674-687**	AFIDPLGLPDRPFY	1621.88
1775.48±1.32	673-687*	RAFIDPLGLPDRPFY	1778.07
2440.2±1.3	653-672	FDKSNPIVLRMMNDQLMFLE	2442.932
1904.63±1.56	672-687*	ERAFIDPLGLPDRPFY	1907.19
2310.6±2.5	653-671	FDKSNPIVLR**MMNDQLMFL**	2313.82
2017.4±1.94	671-687	LERAFIDPLGLPDRPFY	2020.35
2197.43±1.78	653-670	FDKSNPIVL**RMMNDQLMF**	2200.66

Boldface sequence correspond to peptides predicted to bind to MHC, see Table 13.

* On the basis of mass alone this peak could equally well be assigned to a peptide beginning at 654, however proteasomal removal of just the N-terminal amino acid is considered unlikely. If the issue were important it could be resolved by N-terminal sequencing.

** On the basis of mass alone these peaks could have been assigned to internal fragments, but given the overall pattern of digestion it was considered unlikely.

Epitope Identification

Fragments co-C-terminal with 8-10 amino acid long sequences predicted to bind HLA by the SYFPEITHI or NIH algorithms were chosen for further study. The digestion and prediction steps of the procedure can be usefully practiced in any order. Although the substrate peptide used in proteasomal digest described here was specifically designed to include predicted HLA-A2.1

binding sequences, the actual products of digestion can be checked after the fact for actual or predicted binding to other MHC molecules. Selected results are shown in Table 14.

Table 14. Predicted HLA binding by proteasomally generated fragments

SEQ ID NO	PEPTIDE	HLA	SYFPEITHI	NIH
66 & (67)	(R)MMNDQLMFL	A*0201	24 (23)	1360 (722)
		A*0205	NP†	71 (42)
		A26	15	NP
		B*2705	12	50
68	RMMNDQLMF	B*2705	17	75

†No prediction

As seen in Table 14, N-terminal addition of authentic sequence to epitopes can generate still useful, even better epitopes, for the same or different MHC restriction elements. Note for example the pairing of (R)MMNDQLMFL (SEQ ID NOS. 66 and (67)) with HLA-A*02, where the 10-mer retains substantial predicted binding potential.

HLA-A*0201 binding assay

HLA-A*0201 binding studies were preformed, essentially as described in Example 3 above, with $PSMA_{663-671}$, (SEQ ID NO. 66) and $PSMA_{662-671}$, RMMNDQLMFL (SEQ NO. 67). As seen in figures 10, 13 and 14, this epitope exhibits significant binding at even lower concentrations than the positive control peptide (FLPSDYFPSV (HBV_{18-27}); SEQ ID NO: 24). Though not run in parallel, comparison to the controls suggests that $PSMA_{662-671}$ (which approaches the Melan A peptide in affinity) has the superior binding activity of these two PSMA peptides.

Example 8

Vaccinating with epitope vaccines.

1. Vaccination with peptide vaccines:

A. Intranodal delivery

A formulation containing peptide in aqueous buffer with an antimicrobial agent, an antioxidant, and an immunomodulating cytokine, was injected continuously over several days into the inguinal lymph node using a miniature pumping system developed for insulin delivery (MiniMed; Northridge, CA). This infusion cycle was selected in order to mimic the kinetics of antigen presentation during a natural infection.

B. Controlled release

A peptide formulation is delivered using controlled PLGA microspheres as is known in the art, which alter the pharmacokinetics of the peptide and improve immunogenicity. This formulation is injected or taken orally.

C. Gene gun delivery

A peptide formulation is prepared wherein the peptide is adhered to gold microparticles as is known in the art. The particles are delivered in a gene gun, being accelerated at high speed so as to penetrate the skin, carrying the particles into dermal tissues that contain pAPCs.

D. Aerosol delivery

A peptide formulation is inhaled as an aerosol as is known in the art, for uptake into appropriate vascular or lymphatic tissue in the lungs.

2. Vaccination with nucleic acid vaccines:

A nucleic acid vaccine is injected into a lymph node using a miniature pumping system, such as the MiniMed insulin pump. A nucleic acid construct formulated in an aqueous buffered solution containing an antimicrobial agent, an antioxidant, and an immunomodulating cytokine, is delivered over a several day infusion cycle in order to mimic the kinetics of antigen presentation during a natural infection.

Optionally, the nucleic acid construct is delivered using controlled release substances, such as PLGA microspheres or other biodegradable substances. These substances are injected or taken orally. Nucleic acid vaccines are given using oral delivery, priming the immune response through uptake into GALT tissues. Alternatively, the nucleic acid vaccines are delivered using a gene gun, wherein the nucleic acid vaccine is adhered to minute gold particles. Nucleic acid constructs can also be inhaled as an aerosol, for uptake into appropriate vascular or lymphatic tissue in the lungs.

Example 9

Assays for the effectiveness of epitope vaccines.

1. Tetramer analysis:

Class I tetramer analysis is used to determine T cell frequency in an animal before and after administration of a housekeeping epitope. Clonal expansion of T cells in response to an epitope indicates that the epitope is presented to T cells by pAPCs. The specific T cell frequency is measured against the housekeeping epitope before and after administration of the epitope to an animal, to determine if the epitope is present on pAPCs. An increase in frequency of T cells specific to the epitope after administration indicates that the epitope was presented on pAPC.

2. Proliferation assay:

Approximately 24 hours after vaccination of an animal with housekeeping epitope, pAPCs are harvested from PBMCs, splenocytes, or lymph node cells, using monoclonal antibodies against specific markers present on pAPCs, fixed to magnetic beads for affinity purification. Crude blood or splenoctye preparation is enriched for pAPCs using this technique. The enriched pAPCs are

then used in a proliferation assay against a T cell clone that has been generated and is specific for the housekeeping epitope of interest. The pAPCs are coincubated with the T cell clone and the T cells are monitored for proliferation activity by measuring the incorporation of radiolabeled thymidine by T cells. Proliferation indicates that T cells specific for the housekeeping epitope are being stimulated by that epitope on the pAPCs.

3. Chromium release assay:

A human patient, or non-human animal genetically engineered to express human class I MHC, is immunized using a housekeeping epitope. T cells from the immunized subject are used in a standard chromium release assay using human tumor targets or targets engineered to express the same class I MHC. T cell killing of the targets indicates that stimulation of T cells in a patient would be effective at killing a tumor expressing a similar TuAA.

Example 10

Induction of CTL response with naked DNA is efficient by Intra-lymph node immunization.

In order to quantitatively compare the $CD8^+$ CTL responses induced by different routes of immunization a plasmid DNA vaccine (pEGFPL33A) containing a well-characterized immunodominant CTL epitope from the LCMV-glycoprotein (G) (gp33; amino acids 33-41) (Oehen, S., et al.. *Immunology* 99, 163-169 2000) was used, as this system allows a comprehensive assessment of antiviral CTL responses. Groups of 2 C57BL/6 mice were immunized once with titrated doses (200-0.02μg) of pEGFPL33A DNA or of control plasmid pEGFP-N3, administered i.m. (intramuscular), i.d. (intradermal), i.spl. (intrasplenic), or i.ln. (intra-lymph node). Positive control mice received 500 pfu LCMV i.v. (intravenous). Ten days after immunization spleen cells were isolated and gp33-specific CTL activity was determined after secondary *in vitro* restimulation. As shown in Fig. 15, i.m. or i.d. immunization induced weakly detectable CTL responses when high doses of pEFGPL33A DNA (200μg) were administered. In contrast, potent gp33-specific CTL responses were elicited by immunization with only 2μg pEFGPL33A DNA i.spl. and with as little as 0.2μg pEFGPL33A DNA given i.ln. (figure 15; symbols represent individual mice and one of three similar experiments is shown). Immunization with the control pEGFP-N3 DNA did not elicit any detectable gp33-specific CTL responses (data not shown).

Example 11

Intra-lymph node DNA immunization elicits anti-tumor immunity.

To examine whether the potent CTL responses elicited following i.ln. immunization were able to confer protection against peripheral tumors, groups of 6 C57BL/6mice were immunized three times at 6-day intervals with 10μg of pEFGPL33A DNA or control pEGFP-N3 DNA. Five days after the last immunization small pieces of solid tumors expressing the gp33 epitope (EL4-33) were transplanted s.c. into both flanks and tumor growth was measured every 3-4d. Although the

EL4-33 tumors grew well in mice that had been repetitively immunized with control pEGFP-N3 DNA (figure 16), mice which were immunized with pEFGPL33A DNA i.ln. rapidly eradicated the peripheral EL4-33 tumors (figure 16).

Example 12

Differences in lymph node DNA content mirrors differences in CTL response following intra-lymph node and intramuscular injection.

pEFGPL33A DNA was injected i.ln. or i.m. and plasmid content of the injected or draining lymph node was assessed by real time PCR after 6, 12, 24, 48 hours, and 4 and 30 days. At 6, 12, and 24 hours the plasmid DNA content of the injected lymph nodes was approximately three orders of magnitude greater than that of the draining lymph nodes following i.m. injection. No plasmid DNA was detectable in the draining lymph node at subsequent time points (Fig. 17). This is consonant with the three orders of magnitude greater dose needed using i.m. as compared to i.ln. injections to achieve a similar levels of CTL activity. $CD8^{-/-}$ knockout mice, which do not develop a CTL response to this epitope, were also injected i.ln. showing clearance of DNA from the lymph node is not due to $CD8^{+}$ CTL killing of cells in the lymph node. This observation also supports the conclusion that i.ln. administration will not provoke immunopathological damage to the lymph node.

Example 13

Administration of a DNA plasmid formulation of a therapeutic vaccine for melanoma to humans.

A SYNCHROTOPE™ TA2M melanoma vaccine encoding the HLA-A2-restricted tyrosinase epitope SEQ ID NO. 1 and epitope cluster SEQ ID NO. 69, was formulated in 1% Benzyl alcohol, 1% ethyl alcohol, 0.5mM EDTA, citrate-phosphate, pH 7.6. Aliquots of 80, 160, and 320 μg DNA/ml were prepared for loading into MINIMED 407C infusion pumps. The catheter of a SILHOUETTE infusion set was placed into an inguinal lymph node visualized by ultrasound imaging. The assembly of pump and infusion set was originally designed for the delivery of insulin to diabetics and the usual 17mm catheter was substituted with a 31mm catheter for this application. The infusion set was kept patent for 4 days (approximately 96 hours) with an infusion rate of about 25 μl (microliter)/hour resulting in a total infused volume of approximately 2.4 ml. Thus the total administered dose per infusion was approximately 200, and 400 μg; and can be 800 μg, respectively, for the three concentrations described above. Following an infusion subjects were given a 10 day rest period before starting a subsequent infusion. Given the continued residency of plasmid DNA in the lymph node after administration (as in example 12) and the usual kinetics of CTL response following disappearance of antigen, this schedule will be sufficient to maintain the immunologic CTL response.

Example 14

Evaluating Likelihood of Epitope Cross-reactivity on Non-target Tissues.

As noted above PSA is a member of the kallikrein family of proteases, which is itself a subset of the serine protease family. While the members of this family sharing the greatest degree of sequence identity with PSA also share similar expression profiles, it remains possible that individual epitope sequences might be shared with proteins having distinctly different expression profiles. A first step in evaluating the likelihood of undesirable cross-reactivity is the identification of shared sequences. One way to accomplish this is to conduct a BLAST search of an epitope sequence against the SWISSPROT or Entrez non-redundant peptide sequence databases using the "Search for short nearly exact matches" option; hypertext transfer protocol accessible on the world wide web (http://www) at "ncbi.nlm.nih.gov/blast/index.html". Thus searching SEQ ID NO. 104, WVLTAAHCI, against SWISSPROT (limited to entries for homo sapiens) one finds four exact matches, including PSA. The other three are from kallikrein 1 (tissue kallikrein), and elastase 2A and 2B. While these nine amino acid segments are identical, the flanking sequences are quite distinct, particularly on the C-terminal side, suggesting that processing may proceed differently and that thus the same epitope may not be liberated from these other proteins. (Please note that kallikrein naming is confused. Thus, the kallikrein 1 [accession number P06870] is a different protein than the one [accession number AAD13817] mentioned in the paragraph on PSA above in the section on tumor-associated antigens).

This possibility can be tested in several ways. Synthetic peptides containing the epitope sequence embedded in the context of each of these proteins can be subjected to *in vitro* proteasomal digestion and analysis as described above. Alternatively, cells expressing these other proteins, whether by natural or recombinant expression, can be used as targets in a cytotoxicity (or similar) assay using $CD8^+$ T cells that recognize the epitope, in order to determine if the epitope is processed and presented.

Examples 15-67

Epitopes.

The methodologies described above, and in particular in examples 3-7, have been applied to additional synthetic peptide substrates, as summarized in figures 18-70 leading to the identification of further epitopes as set forth the in tables 15-67 below. The substrates used here were generally designed to identify products of housekeeping proteasomal processing that give rise to HLA-A*0201 binding epitopes, but additional MHC-binding reactivities can be predicted, as discussed above. Many such reactivities are disclosed, however, these listings are meant to be exemplary, not exhaustive or limiting. As also discussed above, individual components of the analyses can be used in varying combinations and orders. N-terminal pool sequencing which allows quantitation of various cleavages and can resolve ambiguities in the mass spectrum where necessary, can also be used to identify cleavage sites when digests of substrate yield fragments that do not fly well in MALDI-TOF mass spectrometry. Due to these advantages it was routinely used.

Although it is preferred to identify epitopes on the basis of the C-terminus of an observed fragment, epitopes can also be identified on the basis of the N-terminus of an observed fragment adjacent to the epitope.

Not all of the substrates necessarily meet the formal definition of an epitope cluster as referenced in example 3. Some clusters are so large that it was more convenient to use substrates spanning only a portion of the cluster. In other cases, substrates were extended beyond clusters meeting the formal definition to include neighboring predicted epitopes or were designed around predicted epitopes with no association with any cluster. In some instances, actual binding activity dictated what substrate was made when HLA binding activity was determined for a selection of peptides with predicted affinity, before synthetic substrates were designed.

Figures 18-70 show the results of proteasomal digestion analysis as a mapping of mass spectrum peaks onto the substrate sequence. Each figure presents an individual timepoint from the digestion judged to be respresentative of the overall data, however some epitopes listed in Tables 15-67 were identified based on fragments not observed at the particular timepoints illustrated. The mapping of peaks onto the sequence was informed by N-terminal pool sequencing of the digests, as noted above. Peaks possibly corresponding to more than one fragment are represented by broken lines. Nonetheless, epitope identifications are supported by unambiguous occurrence of the associated cleavage.

Example 15: Tyrosinase 171-203

Table 15

Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
171-179	NIYDLFVWM	108	A0201	17	93.656
			A26	25	N/A
			A3	18	<5
173-182	YDLFVWMHYY	109	A1	17	<5
174-182	DLFVWMHYY	110	A1	16	<5
			A26	30	N/A
			A3	16	27
186-194	DALLGGSEI	111	A0201	17	<5
			B5101	26	440
191-200	GSEIWRDIDF	112	A1	18	67.5
192-200	SEIWRDIDF	113	B08	16	<5
193-201	EIWRDIDFA	114	A26	20	N/A

†Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 18.

Example 16: Tyrosinase 401-427

Table 16

Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
407-416	LQEVYPEANA	115	A0203	18	N/A
409-418	EVYPEANAPI	116	A26	19	N/A
			A3	20	<5
410-418	VYPEANAPI	117	B5101	15	6.921
411-418	YPEANAPI	118	B5101	22	N/A
411-420	YPEANAPIGH	119	A1	16	<5
416-425	APIGHNRESY	120	A1	18	<5
			A26	15	N/A
417-425	PIGHNRESY	121	A1	16	<5
			A26	21	N/A
			A3	17	<5
417-426	PIGHNRESYM	122	A26	19	N/A

†Scores are given from the two binding prediction programs referenced above (see example 3) See also figure 19.

Example 17: Tyrosinase 415-449

Table 17

Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
416-425	APIGHNRESY	120	A1	18	<5
			A26	15	N/A
			A3	17	<5
			B0702	15	N/A
417-425	PIGHNRESY	124	A1	16	<5
			A26	21	N/A
			A3	17	<5
423-430	ESYMVPFI	125	B5101	17	N/A
423-432	ESYMVPFIPL	126	A26	18	N/A
424-432	SYMVPFIPL	127	B0702	16	N/A
424-433	SYMVPFIPLY	128	A1	19	<5
			A26	15	N/A
425-433	YMVPFIPLY	129	A0201	18	<5
			A1	23	5
			A26	17	N/A
426-434	MVPFIPLYR	130	A3	18	<5
426-435	MVPFIPLYRN	131	A26	16	N/A
427-434	VPFIPLYR	132	B5101	18	N/A
430-437	IPLYRNGD	133	B08	16	<5
430-439	IPLYRNGDFF	134	B0702	18	N/A
431-439	PLYRNGDFF	135	A26	18	N/A
			A3	24	<5
431-440	PLYRNGDFFI	136	A0201	16	23.43
			A3	17	<5
434-443	RNGDFFISSK	137	A3	20	<5
435-443	NGDFFISSK	138	A3	15	<5
			B2705	15	5

†Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 20.

Example 18: Tyrosinase 457-484

Table 18

Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
463-471	YIKSYLEQA	139	A0201	18	<5
			A26	17	N/A
466-474	SYLEQASRI	140	B5101	16	<5
469-478	EQASRIWSWL	141	A26	17	N/A
470-478	QASRIWSWL	142	B5101	16	55
471-478	ASRIWSWL	143	B08	16	<5
471-479	ASRIWSWLL	144	B08	16	<5
473-481	RIWSWLLGA	145	A0201	19	13.04
			A26	16	N/A
			A3	15	<5

†Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 21.

Example 19: CEA 92-118

Table 19

Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
92-100	GPAYSGREI	146	B0702	18	8
			B08	15	<5
			B5101	22	484
92-101	GPAYSGREII	147	B0702	18	12
93-100	PAYSGREI	148	B5101	22	N.A.
93-101	PAYSGREII	149	B5101	24	48.4
93-102	PAYSGREIIY	150	A1	19	<5
94-102	AYSGREIIY	151	A1	21	<5
97-105	GREIIYPNA	152	B2705	17	200
			B2709	16	
98-107	REIIYPNASL	153	A0201	16	<5
99-107	EIIYPNASL	154	A0201	21	<5
			A26	28	N.A.
			A3	16	<5
			B0702	15	6
			B08	18	<5
			B2705	16	<5
99-108	EIIYPNASLL	155	A0201	16	<5
			A26	27	N.A.
			A3	17	<5
100-107	IIYPNASL	156	B08	15	<5
100-108	IIYPNASLL	157	A0201	23	15.979
			A26	21	N.A.
			A24	N.A.	<5
			A3	23	<5
			B08	15	<5
			B1510	15	N.A.
			B2705	16	50
			B2709	15	
100-109	IIYPNASLLI	158	A0201	22	7.804
			A3	20	<5
102-109	YPNASLLI	159	B5101	23	N.A.
107-116	LLIQNIIQND	160	A0201	18	<5
			A26	17	N.A.

†Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 22.

Example 20: CEA 131-159

Table 20

Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
132-141	EEATGQFRVY	161	A1	19	<5
			A26	21	N.A.
133-141	EATGQFRVY	162	A1	22	<5
			A26	23	N.A.
			B5101	16	<5
141-149	YPELPKPSI	163	B0702	20	<5
			B5101	22	572
142-149	PELPKPSI	164	B08	16	<5

†Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 23.

Example 21: CEA 225-251

Table 21

Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
225-233	RSDSVILNV	165	A0201	15	<5
			A1	22	<5
			B2709	15	N.A.
225-234	RSDSVILNVL	166	A0201	15	<5
226-234	SDSVILNVL	167	A0201	17	<5
226-235	SDSVILNVLY	168	A1	20	<5
227-235	DSVILNVLY	169	A1	22	<5
			A26	18	N.A.
233-242	VLYGPDAPTI	170	A0201	25	56.754
			A3	23	<5
234-242	LYGPDAPTI	171	A0201	15	<5
			B5101	15	5.72
235-242	YGPDAPTI	172	B5101	22	N.A.
236-245	GPDAPTISPL	173	A0201	15	<5
			B0702	23	24
237-245	PDAPTISPL	174	A0201	15	<5
			A26	16	N.A.
			B2705	15	<5
238-245	DAPTISPL	175	B5101	25	N.A.
239-247	APTISPLNT	176	B0702	20	6
240-249	PTISPLNTSY	177	A1	22	<5
			A26	24	N.A.
241-249	TISPLNTSY	178	A1	20	5
			A26	24	N.A.
			A3	20	<5

†Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 24.

Example 22: CEA 239-270

Table 22

Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
240-249	PTISPLNTSY	179	A1	22	<5
			A26	24	N.A.
241-249	TISPLNTSY	180	A1	20	5
			A26	24	N.A.
			A3	20	<5
246-255	NTSYRSGENL	181	A26	19	N.A.
247-255	TSYRSGENL	182	B2705	15	50
248-255	SYRSGENL	183	B08	18	<5
248-257	SYRSGENLNL	184	B0702	14	<5
249-257	YRSGENLNL	185	A0201	15	<5
			B0702	16	<5
			B2705	27	2000
			B2709	22	N.A.
251-259	SGENLNLSC	186	A1	19	<5
253-262	ENLNLSCHAA	187	A0203	19	<5
254-262	NLNLSCHAA	188	A0201	17	<5

†Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 25.

Example 23: CEA 259-286

Table 23

Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
260-269	HAASNPPAQY	189	A1	15	<5
261-269	AASNPPAQY	190	A1	17	<5
			A3	17	<5
264-273	NPPAQYSWFV	191	B0702	18	<5
265-273	PPAQYSWFV	192	B0702	18	<5
			B5101	19	20
266-273	PAQYSWFV	193	B5101	18	N.A.
272-280	FVNGTFQQS	194	A26	18	N.A.
			A3	15	<5

†Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 26.

Example 24: CEA 309-336

Table 24

Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
310-319	RTTVTTITVY	195	A1	22	<5
			A26	24	N.A.
			A3	15	<5
311-319	TTVTTITVY	196	A1	22	<5
			A26	24	N.A.
			B2705	15	5
319-327	YAEPPKPFI	197	A0201	17	<5
			A1	17	18
			B5101	22	286
319-328	YAEPPKPFIT	198	A1	16	45
320-327	AEPPKPFI	199	B08	16	<5
321-328	EPPKPFIT	200	B5101	16	N.A.
321-329	EPPKPFITS	201	B0702	16	<5
			B5101	16	12.1
322-329	PPKPFITS	202	B08	16	<5

†Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 27.

Example 25: CEA 381-408

Table 25

Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
382-391	SVTRNDVGPY	203	A1	18	<5
			A26	24	N.A.
			A3	21	<5
383-391	VTRNDVGPY	204	A1	23	<5
			A26	24	N.A.
389-397	GPYECGIQN	205	B5101	17	11
391-399	YECGIQNEL	206	A0201	17	<5
			B2705	17	30
394-402	GIQNELSVD	207	A26	15	N.A.
			A3	16	<5

†Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 28.

Example 26: CEA 403-429

Table 26

Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
403-411	HSDPVILNV	208	A0201	17	<5
			A1	26	37.5
403-412	HSDPVILNVL	209	A0201	17	<5
			A1	19	7.5
			A26	15	N.A.
			A24	N.A.	8.064
			B4402	17	N.A.
404-412	SDPVILNVL	210	A0201	17	<5
			B4402	16	N.A.
404-413	SDPVILNVLY	211	A1	20	<5
405-412	DPVILNVL	212	B08	16	<5
			B5101	24	N.A.
405-413	DPVILNVLY	213	A1	18	<5
			A26	18	N.A.
			B5101	16	7.26
408-417	ILNVLYGPDD	214	A3	15	<5
411-420	VLYGPDDPTI	215	A0201	25	56.754
			A3	20	<5
412-420	LYGPDDPTI	216	A0201	15	<5
			A24	N.A.	60
413-420	YGPDDPTI	217	B5101	22	N.A.
417-425	DPTISPSYT	218	B0702	16	<5
418-427	PTISPSYTYY	219	A1	21	<5
			A26	27	N.A.
419-427	TISPSYTYY	220	A1	19	5
			A26	27	N.A.

†Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 29.

Example 27: CEA 416-448

Table 27

Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
418-427	PTISPSYTYY	221	A1	21	<5
			A26	27	N.A.
419-427	TISPSYTYY	222	A1	19	5
			A26	27	N.A.
			A3	18	<5
419-428	TISPSYTYYR	223	A3	15	5.4
424-433	YTYYRPGVNL	224	A0201	18	<5
			A24	N.A.	<5
			A26	20	N.A.
425-433	TYYRPGVNL	225	A0201	14	<5
			A24	N.A.	200
			B0702	16	<5
			B2705	16	5
426-433	YYRPGVNL	226	B08	16	<5
426-435	YYRPGVNLSL	227	A0201	17	<5
			B0702	15	<5
427-435	YRPGVNLSL	228	A0201	17	<5
			B2705	26	2000
			B2709	21	N.A.
428-435	RPGVNLSL	229	B08	17	<5
			B5101	17	N.A.
428-437	RPGVNLSLSC	230	B0702	14	<5
430-438	GVNLSLSCH	231	A26	16	N.A.
			B2705	15	<5
431-440	VNLSLSCHAA	232	A0203	19	N.A.
432-440	NLSLSCHAA	233	A0201	16	<5

†Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 30.

Example 28: CEA 437-464

Table 28

Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
438-447	HAASNPPAQY	234	A1	15	<5
439-447	AASNPPAQY	235	A1	17	<5
			A3	17	<5
442-451	NPPAQYSWLI	236	B0702	17	8
443-451	PPAQYSWLI	237	B0702	17	<5
			B5101	21	40
444-451	PAQYSWLI	238	B5101	20	N.A.
449-458	WLIDGNIQQH	239	A0201	17	<5
			A26	17	N.A.
			A3	21	<5
450-458	LIDGNIQQH	240	A0201	16	<5
			A26	19	N.A.
			A3	17	<5
450-459	LIDGNIQQHT	241	A0201	16	<5
			A26	15	N.A.

†Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 31.

Example 29: CEA 581-607

Table 29

Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
581-590	RSDPVTLDVL	242	A0201	16	<5
			A1	19	7.5
			A26	15	N.A.
			A24	N.A.	9.6
582-590	SDPVTLDVL	243	A0201	16	<5
582-591	SDPVTLDVLY	244	A1	19	<5
583-590	DPVTLDVL	245	B08	16	<5
			B5101	25	N.A.
583-591	DPVTLDVLY	246	A1	17	<5
			A26	18	N.A.
			B5101	16	6
588-597	DVLYGPDTPI	247	A26	16	N.A.
589-597	VLYGPDTPI	248	A0201	25	56.754
			A3	17	6.75
			B5101	17	11.44
596-605	PIISPPDSSY	249	A1	15	<5
			A26	25	N.A.
			A3	22	<5
597-605	IISPPDSSY	250	A1	20	5
			A26	24	N.A.
			A3	24	<5

†Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 32.

Example 30: CEA 595-622

Table 30

Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
597-606	IISPPDSSYL	251	A0201	22	27.464
			A26	21	N.A.
			A3	16	<5
			B0702	14	<5
599-606	SPPDSSYL	252	B08	18	<5
			B5101	17	N.A.
600-608	PPDSSYLSG	253	A1	16	<5
600-609	PPDSSYLSGA	254	B0702	17	<5
602-611	DSSYLSGANL	255	A26	16	N.A.
603-611	SSYLSGANL	256	A0201	15	<5
			B2705	17	50
604-613	SYLSGANLNL	257	A0201	15	<5
			A24	N.A.	300
605-613	YLSGANLNL	258	A0201	25	98.267
			A26	19	N.A.
			A3	15	<5
			B0702	16	<5
			B08	17	<5
			B2705	16	30
610-618	NLNLSCHSA	259	A0201	18	<5

†Scores are given from the two binding prediction programs referenced above (see example 3) See also figure 33.

Example 31: CEA 615-641

Table 31

Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
620-629	NPSPQYSWRI	260	B0702	19	8
622-629	SPQYSWRI	261	B08	15	<5
			B5101	20	N.A.
627-635	WRINGIPQQ	262	B2705	19	20
628-636	RINGIPQQH	263	A3	22	<5
			B2705	16	<5
628-637	RINGIPQQHT	264	A0201	15	<5
631-639	GIPQQHTQV	265	A0201	19	9.563
632-639	IPQQHTQV	266	B5101	20	N.A.

†Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 34.

Example 32: CEA 643-677

Table 32

Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
644-653	KITPNNNGTY	267	A1	20	5
			A26	22	N.A.
			A3	25	<5
645-653	ITPNNNGTY	268	A1	22	<5
			A26	21	N.A.
			A3	14	<5
647-656	PNNNGTYACF	269	A26	15	N.A.
648-656	NNNGTYACF	270	A26	17	N.A.
650-657	NGTYACFV	271	B5101	15	N.A.
661-670	ATGRNNSIVK	272	A3	20	<5
662-670	TGRNNSIVK	273	A3	18	<5
664-672	RNNSIVKSI	274	B2709	15	N.A.
666-674	NSIVKSITV	275	A0201	16	<5

†Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 35.

Example 33: GAGE-1 6-32

Table 33

Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
7-16	STYRPRPRRY	276	A1	23	<5
			A26	21	N/A
			A3	15	<5
8-16	TYRPRPRRY	277	A1	19	<5
			A3	15	<5
10-18	RPRPRRYVE	278	A3	17	<5
			B0702	16	N/A
			B08	20	<5
16-23	YVEPPEMI	279	B5101	15	N/A
22-31	MIGPMRPEQF	280	A26	23	N/A
			A3	19	<5
23-31	IGPMRPEQF	281	B08	15	<5
24-31	GPMRPEQF	282	B5101	16	N/A

†Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 36.

Example 34: GAGE-1 105-131

Table 34

Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
105-114	KTPEEEMRSH	283	A26	18	N/A
106-115	TPEEEMRSHY	284	A1	26	11.25
107-115	PEEEMRSHY	285	A1	26	<5
110-119	EMRSHYVAQT	286	A0201	15	<5
113-121	SHYVAQTGI	287	B5101	15	<5
115-124	YVAQTGILWL	288	A0201	23	108.769
			A26	24	N/A
			A3	15	<5
116-124	VAQTGILWL	289	A0201	22	6.381
			B08	16	<5
			B2705	16	10
			B5101	20	78.65
116-125	VAQTGILWLL	290	A0201	19	8.701
117-125	AQTGILWLL	291	A0201	17	37.362
			B2705	16	200
118-126	QTGILWLLM	292	A26	19	N/A
118-127	QTGILWLLMN	293	A26	15	N/A
120-129	GILWLLMNNC	294	A26	15	N/A
121-129	ILWLLMNNC	295	A0201	15	161.227

†Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 37.

Example 35: GAGE-1 112-137

Table 35

Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
124-131	LLMNNCFL	296	B08	16	<5
123-131	WLLMNNCFL	297	A0201	22	1999.734
			A26	16	N/A
			B08	17	<5
122-130	LWLLMNNCF	298	B2705	15	<5
121-130	ILWLLMNNCF	299	A26	18	N/A
			A3	17	10
121-129	ILWLLMNNC	295	A0201	15	161.227
120-129	GILWLLMNNC	294	A26	15	N/A
118-127	QTGILWLLMN	293	A26	15	N/A
118-126	QTGILWLLM	292	A26	19	N/A
117-125	AQTGILWLL	291	A0201	17	37.362
			B2705	16	200
			B4402	17	N/A
116-125	VAQTGILWLL	290	A0201	19	8.701
116-124	VAQTGILWL	289	A0201	22	6.381
			B08	16	<5
			B2705	16	10
			B4402	15	N/A
			B5101	20	78.65
115-124	YVAQTGILWL	288	A0201	23	108.769
			A26	24	N/A
			A3	15	<5
113-121	SHYVAQTGI	287	B5101	15	<5

†Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 38.

Example 36 MAGE-1 51-77

Table 36

Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
62-70	SAFPTTINF	309	A26	15	N/A
			B4402	18	N/A
			B2705	17	25
61-70	ASAFPTTINF	310	B4402	15	N/A
60-68	GASAFPTTI	311	A0201	16	<5
			B5101	25	220
57-66	SPQGASAFPT	312	B0702	19	N/A

†Scores are given from the two binding prediction programs referenced above. See also figure 39.

Example 37: Mage-1 126-153

Table 37

Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
144-151	FGKASESL	313	B08	21	<5
143-151	IFGKASESL	314	A26	16	N/A
			B2705	15	<5
142-151	EIFGKASESL	315	A0201	20	<5
			A26	29	N/A
			B4402	15	N/A
142-149	EIFGKASE	316	B08	16	<5
133-140	IKNYKHCF	317	B08	18	<5
132-140	VIKNYKHCF	318	A26	21	N/A
			B08	21	<5
131-140	SVIKNYKHCF	319	A26	23	N/A
			A3	18	<5
			B4402	15	N/A
132-139	VIKNYKHC	320	B08	15	<5
131-139	SVIKNYKHC	321	A26	18	N/A
128-136	MLESVIKNY	322	A1	28	45
			A26	24	N/A
			A3	17	<5
			B4402	15	N/A
127-136	EMLESVIKNY	323	A1	15	<5
			A26	23	N/A
			B4402	18	N/A
126-134	AEMLESVIK	324	A3	18	<5
			B2705	15	30
			B4402	16	N/A

†Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 40.

Example 38: MAGE-2 272-299

Table 38

Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
274-283	GPRALIETSY	325	A1	15	<5
275-283	PRALIETSY	326	A1	15	<5
			B2705	23	100
276-284	RALIETSYV	327	A0201	18	19.658
			B5101	20	55
277-286	ALIETSYVKV	328	A0201	30	427.745
			A26	18	N/A
			A3	21	<5
278-286	LIETSYVKV	329	A0201	23	<5
			A26	17	N/A
			B5101	15	<5
278-287	LIETSYVKVL	330	A0201	22	<5
			A26	22	N/A
279-287	IETSYVKVL	331	A0201	15	<5
			B1510	15	N/A
			B5101	15	<5
280-289	ETSYVKVLH H	332	A26	21	N/A
282-291	SYVKVLHHT L	333	A0201	15	<5
283-291	YVKVLHHTL	334	A0201	19	<5
			A26	20	N/A
			A3	15	<5
			B08	21	<5
285-293	KVLHHTLKI	335	A0201	20	11.822
			A3	18	<5
			B5101	15	<5

†Scores are given from the two binding prediction programs referenced above (see example 3).] See also figure 41.

Example 39 MAGE-2 287-314

Table 39

Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
303-311	PLHERALRE	336	A3	19	<5
			B08	16	<5
302-309	PPLHERAL	337	B08	16	<5
			B5101	18	N/A
301-309	YPPLHERAL	338	B0702	21	N/A
			B08	18	<5
			B4402	15	N/A
			B5101	20	143
300-309	SYPPLHERAL	339	A0201	15	<5
			B4402	18	N/A
299-307	ISYPPLHER	340	B2705	17	25
298-307	HISYPPLHER	341	A26	15	N/A
292-299	KIGGEPHI	342	B5101	15	N/A
291-299	LKIGGEPHI	343	A0201	17	<5
290-299	TLKIGGEPHI	344	A0201	18	<5

†Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 42.

Example 40 Mage-3 287-314

Table 40

Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
303-311	PLHEWVLRE	345	A26	15	N/A
302-309	PPLHEWVL	346	B08	16	<5
			B5101	19	N/A
301-309	YPPLHEWVL	347	B0702	21	N/A
			B08	17	<5
			B5101	22	130
301-308	YPPLHEWV	348	B5101	22	N/A
300-308	SYPPLHEWV	349	A0201	15	<5
299-308	ISYPPLHEWV	350	A0201	15	6.656
298-307	HISYPPLHEW	351	A26	15	N/A
293-301	ISGGPHISY	352	A1	25	<5
292-301	KISGGPHISY	353	A1	20	<5
			A26	23	N/A
			A3	21	5.4

†Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 43.

Example 41: Melan-A 44-71

Table 41

Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
45-54	CWYCRRRNGY	354	A1	16	<5
46-54	WYCRRRNGY	355	A1	16	<5
47-55	YCRRRNGYR	356	B08	15	<5
49-57	RRRNGYRAL	357	B08	17	<5
			B2705	26	1800
			B2709	24	N/A
51-60	RNGYRALMDK	358	A3	15	<5
52-60	NGYRALMDK	359	A3	18	<5
55-63	RALMDKSLH	360	B2705	16	<5
56-63	ALMDKSLH	361	B08	16	<5
55-64	RALMDKSLHV	362	A0201	17	<5
56-64	ALMDKSLHV	363	A0201	26	1055.104
			A3	18	<5
			B08	16	<5

†Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 44.

Example 42: PRAME 274-301

Table 42

Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
275-284	YISPEKEEQY	364	A1	21	5
			A26	23	N/A
			A3	20	<5
			B4402	15	N/A
276-284	ISPEKEEQY	365	A1	19	<5
			A26	15	N/A
277-285	SPEKEEQYI	366	B0702	17	N/A
			B5101	21	484
278-285	PEKEEQYI	367	B08	18	<5
279-288	EKEEQYIAQF	368	A26	24	N/A
			B4402	16	N/A
280-288	KEEQYIAQF	369	A26	17	N/A
			B2705	19	45
			B4402	25	N/A
283-292	QYIAQFTSQF	370	A3	17	<5
			B4402	15	N/A
284-292	YIAQFTSQF	371	A0201	15	<5
			A26	24	N/A
			A3	19	<5
284-293	YIAQFTSQFL	372	A0201	22	74.314
			A26	21	N/A
285-293	IAQFTSQFL	373	A0201	15	<5
			B08	15	<5
			B5101	19	78.65
286-295	AQFTSQFLSL	374	A0201	16	15.226
			A26	15	N/A
			B0702	15	N/A
			A4402	18	N/A
287-295	QFTSQFLSL	375	A26	21	N/A
290-298	SQFLSLQCL	376	A0201	17	18.432
			A26	16	N/A
			B2705	16	1000
			B4402	15	N/A

†Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 45.

Example 43: PRAME 434-463

Table 43

Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
439-448	VLYPVPLESY	377	A0201	20	<5
			A1	21	5
			A26	25	N/A
			A3	25	67.5
440-448	LYPVPLESY	378	A1	16	<5
446-455	ESYEDIHGTL	379	A26	16	N/A
448-457	YEDIHGTLHL	380	A1	18	<5
449-457	EDIHGTLHL	381	B2705	15	<5
451-460	IHGTLHLERL	382	A0201	16	<5

†Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 46.

Example 44: PRAME 452-480

Table 44

Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
454-463	TLHLERLAYL	383	A0201	26	270.234
			A26	21	N/A
455-463	LHLERLAYL	384	A0201	22	<5
			B08	20	<5
			B1510	21	N/A
			B2705	15	<5
456-463	HLERLAYL	385	B08	17	<5
456-465	HLERLAYLHA	386	A3	16	<5
			A1	17	<5
458-467	ERLAYLHARL	387	A26	16	N/A
459-467	RLAYLHARL	388	A0201	24	21.362
			B08	17	<5
			B2705	18	90
			B2709	15	N/A
459-468	RLAYLHARLR	389	A3	22	<5
460-467	LAYLHARL	390	B08	15	<5
			B5101	20	N/A
460-468	LAYLHARLR	391	B5101	18	<5
461-470	AYLHARLREL	392	A0201	20	<5
			B4402	16	N/A
462-470	YLHARLREL	393	A0201	28	45.203
			B08	25	8
462-471	YLHARLRELL	394	A0201	22	48.151
			A26	16	N/A
463-471	LHARLRELL	395	A0201	15	<5
			B1510	22	N/A
464-471	HARLRELL	396	B08	30	320
			B5101	17	N/A
464-472	HARLRELLC	397	B08	20	16
469-478	ELLCELGRPS	398	A3	15	<5
470-478	LLCELGRPS	399	A0201	15	<5

†Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 47.

Example 45: PSA 143-169

Table 45

Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
144-153	QEPALGTTCY	400	A1	15	<5
145-153	EPALGTTCY	401	A1	17	<5
			A26	17	N/A

†Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 48.

Example 46: PSA 156-1883

Table 46

Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
162-171	PEEFLTPKKL	402	B4402	24	N.A.
163-171	EEFLTPKKL	403	A26	17	N.A.
			B4402	29	N.A.
165-173	FLTPKKLQC	404	A3	20	<5
			B08	17	<5
165-174	FLTPKKLQCV	405	A0201	26	735.86
			A26	15	N.A.
166-174	LTPKKLQCV	406	A0201	21	<5
			A26	18	N.A.
167-174	TPKKLQCV	407	B08	16	<5
			B5101	22	N.A.
167-175	TPKKLQCVD	408	B5101	15	<5
170-179	KLQCVDLHVI	409	A0201	24	34.433
			A3	17	<5
171-179	LQCVDLHVI	410	A0201	15	<5
			B5101	16	6.292

†Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 49.

Example 47: PSCA 67-94

Table 47

Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
73-81	DSQDYYVGK	411	A3	15	<5
74-82	SQDYYVGKK	412	A1	16	<5
74-83	SQDYYVGKKN	413	A1	15	<5
76-84	DYYVGKKNI	414	B5101	19	23.426
77-84	YYVGKKNI	415	B08	16	<5
78-86	YVGKKNITC	416	A3	15	<5
78-87	YVGKKNITCC	417	A26	15	N/A

†Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 50.

Example 48: PSMA 378-405

Table 48

Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
381-390	WVFGGIDPQS	418	A26	16	N/A
			A3	15	<5
385-394	GIDPQSGAAV	419	A0201	24	<5
			A0203	17	N/A
			A1	15	10
			A26	15	N/A
			A3	18	<5
386-394	IDPQSGAAV	420	A0201	15	<5
387-394	DPQSGAAV	421	B5101	22	N/A
387-395	DPQSGAAVV	422	B0702	18	N/A
			B5101	26	440
387-396	DPQSGAAVVH	423	A3	15	<5
388-396	PQSGAAVVH	424	A3	17	<5
389-398	QSGAAVVHEI	425	A0201	15	<5
390-398	SGAAVVHEI	426	A0201	19	<5
			B5101	21	88
391-398	GAAVVHEI	427	B5101	23	N/A
391-399	GAAVVHEIV	428	A0201	17	<5
			B5101	20	133.1
392-399	AAVVHEIV	429	B5101	19	N/A

†Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 51.

Example 49: PSMA 597-623

Table 49

Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
597-605	CRDYAVVLR	430	B2705	22	N/A
598-607	RDYAVVLRKY	431	A1	17	<5
			A26	15	N/A
			A3	16	<5
599-607	DYAVVLRKY	432	A1	19	<5
			A26	22	N/A
600-607	YAVVLRKY	433	B5101	17	N/A
602-611	VVLRKYADKI	434	A0201	17	<5
			A3	18	<5
603-611	VLRKYADKI	435	A0201	22	<5
			A3	16	<5
			B08	19	<5
			B5101	16	5.72
603-612	VLRKYADKIY	436	A1	17	<5
			A26	19	N/A
			A3	19	<5
604-611	LRKYADKI	437	B08	17	<5
604-612	LRKYADKIY	438	A1	15	<5
			B2705	19	N/A
605-614	RKYADKIYSI	439	A0201	16	<5
606-614	KYADKIYSI	440	A0201	20	<5
			B08	17	<5
607-614	YADKIYSI	441	B5101	27	N/A

†Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 52.

Example 50: PSMA 615-642

Table 50

Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
616-625	MKHPQEMKTY	442	A1	19	<5
			A26	16	N/A
617-625	KHPQEMKTY	443	A1	15	<5
			A26	16	N/A
618-627	HPQEMKTYSV	444	A0201	15	<5
			B0702	17	N/A

†Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 53.

Example 51: SCP-1 57-86

Table 51

Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
62-71	IDSDPALQKV	445	A0201	19	<5
63-71	DSDPALQKV	446	A0201	17	<5
			A1	20	7.5
			A26	15	N/A
			B5101	15	5.324
67-76	ALQKVNFLPV	447	A0201	23	132.149
			A3	16	<5
70-78	KVNFLPVLE	448	A3	18	<5
71-80	VNFLPVLEQV	449	A0201	16	<5
72-80	NFLPVLEQV	450	A0201	18	<5
75-84	PVLEQVGNSD	451	A3	18	<5
76-84	VLEQVGNSD	452	A1	15	<5
			A3	16	<5

†Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 54.

Example 52: SCP-1 201-227

Table 52

Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
202-210	YEREETRQV	453	A0201	16	<5
202-211	YEREETRQVY	454	A1	19	<5
			A3	15	<5
			A4402	22	N/A
203-211	EREETRQVY	455	A1	27	<5
			A26	19	N/A
			B2705	20	N/A
203-212	EREETRQVYM	456	A26	17	N/A
204-212	REETRQVYM	457	B2705	15	N/A
211-220	YMDLNSNIEK	458	A1	17	25
213-221	DLNSNIEKM	459	A0201	20	<5
			A26	28	N/A
216-226	SNIEKMITAF	460	A26	19	N/A
			B4402	19	N/A
217-225	NIEKMITAF	461	A26	26	N/A
			B2705	17	N/A
			B4402	16	N/A
218-225	IEKMITAF	462	B08	17	<5

†Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 55.

Example 53: SCP-1 395-424

Table 53

Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
397-406	RLENYEDQLI	463	A0201	17	<5
			A3	15	<5
398-406	LENYEDQLI	464	B4402	19	N/A
398-407	LENYEDQLII	465	B4402	19	N/A
399-407	ENYEDQLII	466	B5101	17	19.36
399-408	ENYEDQLIIL	467	A26	20	N/A
400-408	NYEDQLIIL	468	A1	16	<5
400-409	NYEDQLIILT	469	A1	16	<5
401-409	YEDQLIILT	470	A1	18	<5
			B4402	16	N/A
401-410	YEDQLIILTM	471	A1	18	<5
			B4402	16	N/A
402-410	EDQLIILTM	472	A26	18	N/A
			B2705	15	<5
406-415	IILTMELQKT	473	A0201	22	14.824
			A26	16	N/A
407-415	ILTMELQKT	474	A0201	21	29.137

†Scores are given from the two binding prediction programs referenced above (see example 3).. See also figure 56.

Example 54: SCP-1 416-442

Table 54

Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
424-432	KLTNNKEVE	475	A3	18	<5
424-433	KLTNNKEVEL	476	A0201	24	74.768
			A26	18	N/A
			A3	18	<5
425-433	LTNNKEVEL	477	A0201	22	<5
			A26	21	N/A
			B08	22	<5
429-438	KEVELEELKK	478	A3	17	<5
430-438	EVELEELKK	479	A1	18	90
			A26	17	N/A
			A3	24	<5
			B2705	15	<5
430-439	EVELEELKKV	480	A0201	15	<5
			A26	21	N/A
431-439	VELEELKKV	481	A0201	20	80.217
			A4402	15	N/A
			B5101	17	<5

†Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 57.

Example 55: SCP-1 518-545

Table 55

Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
530-539	ETSDMTLELK	482	A26	21	N/A
531-539	TSDMTLELK	483	A1	16	15

†Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 58.

Example 56: SCP-1 545-578

Table 56

Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
548-556	NKKQEERML	484	B08	20	<5
553-562	ERMLTQIENL	485	A26	19	N/A
			B4402	17	N/A
554-562	RMLTQIENL	486	A0201	24	64.335
			B2705	21	150
			B2709	17	N/A
			B4402	15	N/A
555-562	MLTQIENL	487	B08	16	<5
555-564	MLTQIENLQE	488	A3	16	<5
560-569	ENLQETETQL	489	A26	16	N/A
561-569	NLQETETQL	490	A0201	22	87.586
			A26	19	N/A
			A3	15	<5
			B08	18	<5
561-570	NLQETETQLR	491	A3	15	6

†Scores are given from the two binding prediction programs referenced above (see example 3).. See also figure 59.

Example 57: SCP-1 559-585

Table 57

Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
567-576	TQLRNELEYV	492	A0201	16	161.729
568-576	QLRNELEYV	493	A0201	24	32.765
			A3	16	<5
571-580	NELEYVREEL	494	A0201	16	<5
			B4402	23	N/A
572-580	ELEYVREEL	495	A0201	17	<5
			A26	23	N/A
			B08	20	<5
573-580	LEYVREEL	496	B08	19	<5
574-583	EYVREELKQK	497	A3	16	<5
575-583	YVREELKQK	498	A26	17	N/A
			A3	27	<5

†Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 60.

Example 58: SCP-1 665-701

Table 58

Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
675-684	LLEEVEKAK V	499	A0201	27	31.026
676-684	LEEVEKAKV	500	A0201	15	<5
676-685	LEEVEKAKVI	501	A4402	22	N/A
677-685	EEVEKAKVI	502	B08	21	<5
			B4402	24	N/A
			B5101	18	<5
681-690	KAKVIADEA V	503	A0201	15	<5
683-692	KVIADEAVK L	504	A0201	21	6.542
			A26	22	N/A
			A3	25	<5
			B4402	17	N/A
684-692	VIADEAVKL	505	A0201	26	20.473
			A26	22	N/A
			A3	17	<5
			B08	16	<5
			B2705	15	N/A
685-692	IADEAVKL	506	B08	17	<5
			B5101	21	N/A

†Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 61.

Example 59: SCP-1 694-720

Table 59

Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
694-702	KEIDKRCQH	507	A3	16	<5
			A4402	17	N/A
694-703	KEIDKRCQHK	508	A3	17	<5
			B4402	15	N/A
695-703	EIDKRCQHK	509	A26	20	N/A
			A3	20	<5
695-704	EIDKRCQHKI	510	A0201	16	<5
			A26	19	N/A
696-704	IDKRCQHKI	511	B08	17	<5
697-704	DKRCQHKI	512	B5101	16	N/A
698-706	KRCQHKIAE	513	B2705	16	60
698-707	KRCQHKIAEM	514	A26	15	N/A
699-707	RCQHKIAEM	515	A26	15	N/A
			B2705	18	9
701-710	QHKIAEMVAL	516	A26	15	N/A
702-710	HKIAEMVAL	517	A0201	15	<5
			A26	16	N/A
			B4402	16	N/A
703-710	KIAEMVAL	518	B08	16	<5

†Scores are given from the two binding prediction programs referenced

[0386] above (see example 3)

[0387] See also figure 62.

Example 60: SCP-1 735-769

Table 60

Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
737-746	QEQSSLRASL	519	B4402	21	N.A.
738-746	EQSSLRASL	520	A26	22	N.A.
			B0702	15	6
739-746	QSSLRASL	521	B08	19	<5
741-750	SLRASLEIEL	522	A0201	24	<5
			A26	17	N.A.
			A3	16	<5
742-750	LRASLEIEL	523	A0201	17	<5
			B2705	23	2000
			B2709	21	N.A.
743-750	RASLEIEL	524	B5101	17	N.A.
744-753	ASLEIELSNL	525	A0201	20	<5
			A26	16	N.A.
745-753	SLEIELSNL	526	A0201	25	<5
			A26	22	N.A.
			A3	15	<5
			B08	18	<5
745-754	SLEIELSNLK	527	A1	15	18
			A3	22	20
746-754	LEIELSNLK	528	B2705	16	30
			B4402	15	N.A.
747-755	EIELSNLKA	529	A1	19	<5
			A26	18	N.A.
749-758	ELSNLKAELL	530	A0201	17	<5
			A26	22	N.A.
750-758	LSNLKAELL	531	B08	21	<5
751-760	SNLKAELLSV	532	A0201	21	<5
752-760	NLKAELLSV	533	A0201	26	5.599
			A3	18	<5
			B08	16	<5
752-761	NLKAELLSVK	534	A3	30	30
753-761	LKAELLSVK	535	A3	19	<5
753-762	LKAELLSVKK	536	A3	16	<5
754-762	KAELLSVKK	537	A3	18	<5
			B2705	18	30
755-763	AELLSVKKQ	538	B4402	19	N.A.

†Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 63.

Example 61: SCP-1 786-816

Table 61

Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
787-796	EKKDKKTQTF	539	A26	19	N/A
			B4402	15	N/A
788-796	KKDKKTQTF	540	B08	16	<5
			B2705	16	<5
789-796	KDKKTQTF	541	B08	16	<5
797-806	LLETPDIYWK	542	A0201	16	<5
			A3	21	90
798-806	LETPDIYWK	543	B2705	15	30
			B4402	16	N/A
798-807	LETPDIYWKL	544	A0201	15	7.944
			A26	15	N/A
			A4402	24	N/A
799-807	ETPDIYWKL	545	A26	31	N/A
			B4402	16	N/A
800-807	TPDIYWKL	546	B08	16	<5
			B5101	19	N/A

†Scores are given from the two binding prediction programs referenced

[0390] above (see example 3)

[0391] See also figure 64.

Example 62: SCP-1 806-833

Table 62

Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
809-817	SKAVPSQTV	547	A0201	17	<5
810-817	KAVPSQTV	548	B5101	19	N/A
812-821	VPSQTVSRNF	549	B0702	18	N/A
815-824	QTVSRNFTSV	550	A0201	16	<5
			A26	16	N/A
816-824	TVSRNFTSV	551	A0201	16	11.426
			A26	15	N/A
			A3	16	<5
816-825	TVSRNFTSVD	552	A3	20	<5
823-832	SVDHGISKDK	553	A3	21	<5

†Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 65.

Example 63: SCP-1 826-853

Table 63

Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
829-838	SKDKRDYLWT	554	A1	18	<5
832-840	KRDYLWTSA	555	B2705	16	600
832-841	KRDYLWTSAK	556	A3	17	<5
833-841	RDYLWTSAK	557	A3	23	<5
			B2705	18	15
835-843	YLWTSAKNT	558	A0201	16	284.517
835-844	YLWTSAKNTL	559	A0201	26	815.616
			A26	16	N/A
837-844	WTSAKNTL	560	B08	20	<5
841-850	KNTLSTPLPK	561	A3	18	<5
842-850	NTLSTPLPK	562	A3	16	<5

†Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 66.

Example 64: SCP-1 832-859

Table 64

Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
832-840	KRDYLWTSA	563	B2705	16	600
832-841	KRDYLWTSAK	564	A3	17	<5
833-841	RDYLWTSAK	565	A3	23	<5
			B2705	18	15
835-843	YLWTSAKNT	566	A0201	16	284.517
839-846	SAKNTLST	567	B08	16	<5
841-850	KNTLSTPLPK	568	A3	18	<5
842-850	NTLSTPLPK	569	A3	16	<5
843-852	TLSTPLPKAY	570	A1	16	<5
			A26	19	N/A
			A3	18	<5
			B4402	17	N/A
844-852	LSTPLPKAY	571	A1	23	7.5
			A4402	18	N/A

†Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 67.

Example 65: SSX-2 1-27

Table 65

Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
5-12	DAFARRPT	572	B5101	18	N/A
7-15	FARRPTVGA	573	A0201	15	<5
8-17	ARRPTVGAQI	574	A3	18	<5
9-17	RRPTVGAQI	575	B2705	23	1800
			B2709	23	N/A
10-17	RPTVGAQI	576	B5101	20	N/A
13-21	VGAQIPEKI	577	B5101	20	125.84
14-21	GAQIPEKI	578	B5101	25	N/A
15-24	AQIPEKIQKA	579	A0201	16	<5
16-24	QIPEKIQKA	580	A0201	21	6.442
			A26	20	N/A
			B08	17	<5
16-25	QIPEKIQKAF	581	A26	24	N/A
			A3	16	<5
17-24	IPEKIQKA	582	B5101	19	N/A
17-25	IPEKIQKAF	583	B0702	19	N/A
			B08	15	<5
			B2705	16	<5
18-25	PEKIQKAF	584	B08	16	<5

†Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 68.

Example 66: Survivin 116-142

Table 66

Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
116-124	ETNNKKKEF	585	A26	28	N/A
			B08	20	<5
117-124	TNNKKKEF	586	B08	16	<5
122-131	KEFEETAKKV	587	A0201	15	71.806
123-131	EFEETAKKV	588	A26	15	N/A
			B5101	15	5.324
127-134	TAKKVRRA	589	B5101	17	N/A
126-134	ETAKKVRRA	590	A26	24	N/A
128-136	AKKVRRAIE	591	B08	19	<5
129-138	KKVRRAIEQL	592	A0201	15	<5
130-138	KVRRAIEQL	593	A0201	19	<5
			A26	23	N/A
			A3	22	<5
			B08	17	<5
			B2705	16	30
130-139	KVRRAIEQLA	594	A3	19	<5
131-138	VRRAIEQL	595	B08	17	<5

†Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 69.

Example 67: BAGE 1-35

Table 67

Preferred Epitopes Revealed by Housekeeping Proteasome Digestion

Epitope	Sequence	Sequence ID No.	HLA type	HLA binding predictions†	
				SYFPEITHI	NIH
24-31	SPVVSWRL	596	B08	19	<5
			B5101	17	N/A
21-29	KEESPVVSW	597	B4402	23	N/A
19-27	LMKEESPVV	598	A0201	22	5.024
			B5101	15	<5
18-27	RLMKEESPVV	599	A0201	22	105.51
			A3	18	<5
18-26	RLMKEESPV	600	A0201	21	257.342
			A3	17	<5
14-22	LLQARLMKE	601	A0201	18	<5
			A3	15	<5
13-22	QLLQARLMKE	602	A0201	18	<5
			A26	15	N/A
			A3	15	<5

†Scores are given from the two binding prediction programs referenced above (see example 3). See also figure 70.

Example 68

Epitope Clusters.

Known and predicted epitopes are generally not evenly distributed across the sequences of protein antigens. As referred to above, we have defined segments of sequence containing a higher than average density of (known or predicted) epitopes as epitope clusters. Among the uses of epitope clusters is the incorporation of their sequence into substrate peptides used in proteasomal digestion analysis as described herein, or to otherwise inform the selection and design of such substrates. Epitope clusters can also be useful as vaccine components. Fuller discussions of the definition and uses of epitope clusters is found in PCT Publication No. WO 01/82963; PCT Publication No. WO 03/057823; and U.S. Patent Application No. 09/561,571 entitled EPITOPE CLUSTERS and in U.S. Patent Application No. 10/026,066 entitled "EPITOPE SYNCHRONIZATION IN ANTIGEN PRESENTING CELLS." Epitopes and epitope clusters for many of the TAA mentioned herein have been previously disclosed in PCT Publication No. WO 02/081646; in Patent Application No. 09/561,571; in U.S. Patent Application No. 10/117,937; U.S. Provisional Application Nos. 60/337,017 filed on November 7, 2001, and 60/363,210 filed on March 7, 2002, all entitled EPITOPE SEQUENCES. The teachings and embodiments disclosed in said publications and applications are contemplated as supporting principals and embodiments related to and useful in connection with the present invention.

For the TuAAs survivin (SEQ ID NO. 98) and GAGE-1 (SEQ ID NO. 96) the following tables (68-73) present 9-mer epitopes predicted for HLA-A2 binding using both the SYFPEITHI and NIH algorithms and the epitope density of regions of overlapping epitopes, and of epitopes in the whole protein, and the ratio of these two densities. (The ratio must exceed one for there to be a cluster by the above definition; requiring higher values of this ratio reflect preferred embodiments). Individual 9-mers are ranked by score and identified by the position of their first amino in the complete protein sequence. Each potential cluster from a protein is numbered. The range of amino acid positions within the complete sequence that the cluster covers is indicated, as are the rankings of the individual predicted epitopes it is made up of.

Table 68

HLA-A2 Epitope cluster analysis for Survivin (NIH algorithm)
Length of protein sequence: 142 amino acids
Number of 9-mers: 134
Number of 9-mers with NIH score = 5: 2

Cluster	AA	Peptide Rank	Start Position	Score	Peptides/AAs Cluster	Peptides/AAs Whole Pro.	Ratio
1	13-28	1	13	10.26	0.125	0.014	8.875
SEQ ID NO:603		2	20	4.919			

Table 69

HLA-A2 Epitope cluster analysis for Survivin (SYFPEITHI algorithm)
Length of protein sequence: 142 amino acids
Number of 9-mers: 134
Number of 9-mers with SYFPEITHI score = 15: 10

Cluster	AA	Peptide Rank	Start Position	Score	Peptides/AAs Cluster	Whole Pro.	Ratio
1	13-28	5	13	17	0.125	0.070	1.775
SEQ ID NO:603		4	20	18			
2	79-111	8	79	15	0.182	0.070	2.597
SEQ ID NO:604		9	81	15			
		6	88	17			
		1	96	23			
		7	97	16			
		10	103	15			
3	130-141	2	130	19	0.167	0.070	2.381
SEQ ID NO:605		3	133	19			

Table 70

HLA-A2 Epitope cluster analysis for GAGE-1 (NIH algorithm)
Length of protein sequence: 138 amino acids
Number of 9-mers: 130
Number of 9-mers with NIH score = 5: 5

Cluster	AA	Peptide Rank	Start Position	Score	Peptides/AAs Cluster	Whole Pro.	Ratio
1	116-133	1	123	1999.734	0.278	0.036	7.667
SEQ ID NO:606		2	121	161.227			
		3	125	49.834			
		4	117	37.362			
		5	116	6.381			

Table 71

HLA-A2 Epitope cluster analysis for GAGE-1 (SYFPEITHI algorithm)
Length of protein sequence: 138 amino acids
Number of 9-mers: 130
Number of 9-mers with SYFPEITHI score = 5: 6

Cluster	AA	Peptide Rank	Start Position	Score	Peptides/AAs Cluster	Whole Pro.	Ratio
1	116-133	1	116	22	0.333	0.043	7.667
SEQ ID NO:606		2	123	22			
		3	125	22			
		4	117	17			
		5	120	16			
		6	121	15			

Table 72

HLA-A2 Epitope cluster analysis for BAGE (NIH algorithm)

Length of protein sequence: 43 amino acids
Number of 9-mers included: 35
Number of 9-mers with NIH score = 5: 4

Cluster	AA	Peptide Rank	Start Position	Score	Peptides/AAs Cluster	Peptides/AAs Whole Pro.	Ratio
1	7-17	2	7	98.267	0.182	0.093	1.955
SEQ ID NO:607		3	9	11.426			
2	18-27	1	18	257.342	0.200	0.093	2.151
SEQ ID NO:608		4	19	5.024			

Table 73

HLA-A2 Epitope cluster analysis for BAGE (SYFPEITHI algorithm)

Length of protein sequence: 43 amino acids
Number of 9-mers included: 35
Number of 9-mers with SYFPEITHI score = 15: 10

Cluster	AA	Peptide Rank	Start Position	Score	Peptides/AAs Cluster	Peptides/AAs Whole Pro.	Ratio
1	2-27	6	2	18	0.308	0.233	1.323
SEQ ID NO:609		9	6	16			
		1	7	23			
		3	9	21			
		5	11	19			
		7	14	18			
		4	18	21			
		2	19	22			
2	30-39	8	30	17	0.200	0.233	0.858
SEQ ID NO:610		10	31	15			

[0406] The embodiments of the invention are applicable to and contemplate variations in the sequences of the target antigens provided herein, including those disclosed in the various databases that are accessible by the world wide web. Specifically for the specific sequences disclosed herein, variation in sequences can be found by using the provided accession numbers to access information for each antigen.

```
TYROSINASE PROTEIN; SEQ ID NO 2

       1 MLLAVLYCLL  WSFQTSAGHF  PRACVSSKNL  MEKECCPPWS  GDRSPCGQLS
    GRGSCQNILL
        61 SNAPLGPQFP  FTGVDDRESW  PSVFYNRTCQ  CSGNFMGFNC  GNCKFGFWGP
NCTERRLLVR
```

121 RNIFDLSAPE KDKFFAYLTL AKHTISSDYV IPIGTYGQMK NGSTPMFNDI NIYDLFVWMH
181 YYVSMDALLG GSEIWRDIDF AHEAPAFLPW HRLFLLRWEQ EIQKLTGDEN FTIPYWDWRD
241 AEKCDICTDE YMGGQHPTNP NLLSPASFFS SWQIVCSRLE EYNSHQSLCN GTPEGPLRRN
301 PGNHDKSRTP RLPSSADVEF CLSLTQYESG SMDKAANFSF RNTLEGFASP LTGIADASQS
361 SMHNALHIYM NGTMSQVQGS ANDPIFLLHH AFVDSIFEQW LRRHRPLQEV YPEANAPIGH
421 NRESYMVPFI PLYRNGDFFI SSKDLGYDYS YLQDSDPDSF QDYIKSYLEQ ASRIWSWLLG
481 AAMVGAVLTA LLAGLVSLLC RHKRKQLPEE KQPLLMEKED YHSLYQSHL

SSX-2 PROTEIN; SEQ ID NO 3

1 MNGDDAFARR PTVGAQIPEK IQKAFDDIAK YFSKEEWEKM KASEKIFYVY MKRKYEAMTK
61 LGFKATLPPF MCNKRAEDFQ GNDLDNDPNR GNQVERPQMT FGRLQGISPK IMPKKPAEEG
121 NDSEEVPEAS GPQNDGKELC PPGKPTTSEK IHERSGPKRG EHAWTHRLRE RKQLVIYEEI
181 SDPEEDDE

PSMA PROTEIN; SEQ ID NO 4

1 MWNLLHETDS AVATARRPRW LCAGALVLAG GFFLLGFLFG WFIKSSNEAT NITPKHNMKA
61 FLDELKAENI KKFLYNFTQI PHLAGTEQNF QLAKQIQSQW KEFGLDSVEL AHYDVLLSYP
121 NKTHPNYISI INEDGNEIFN TSLFEPPPPG YENVSDIVPP FSAFSPQGMP EGDLVYVNYA
181 RTEDFFKLER DMKINCSGKI VIARYGKVFR GNKVKNAQLA GAKGVILYSD PADYFAPGVK
241 SYPDGWNLPG GGVQRGNILN LNGAGDPLTP GYPANEYAYR RGIAEAVGLP SIPVHPIGYY
301 DAQKLLEKMG GSAPPDSSWR GSLKVPYNVG PGFTGNFSTQ KVKMHIHSTN EVTRIYNVIG
361 TLRGAVEPDR YVILGGHRDS WVFGGIDPQS GAAVVHEIVR SFGTLKKEGW RPRRTILFAS
421 WDAEEFGLLG STEWAEENSR LLQERGVAYI NADSSIEGNY TLRVDCTPLM YSLVHNLTKE
481 LKSPDEGFEG KSLYESWTKK SPSPEFSGMP RISKLGSGND FEVFFQRLGI ASGRARYTKN
541 WETNKFSGYP LYHSVYETYE LVEKFYDPMF KYHLTVAQVR GGMVFELANS IVLPFDCRDY
601 AVVLRKYADK IYSISMKHPQ EMKTYSVSFD SLFSAVKNFT EIASKFSERL QDFDKSNPIV
661 LRMMNDQLMF LERAFIDPLG LPDRPFYRHV IYAPSSHNKY AGESFPGIYD ALFDIESKVD
721 PSKAWGEVKR QIYVAAFTVQ AAAETLSEVA

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ACCESSION NM_000372
VERSION NM_000372.1 GI:4507752
SEQ ID NO 2
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EQEIQKLTGDENFTIPYWDWRDAEKCDICTDEYMGGQHPTNPNLLSPASFFSSWQIVC

SRLEEYNSHQSLCNGTPEGPLRRNPGNHDKSRTPRLPSSADVEFCLSLTQYESGSMDK

AANFSFRNTLEGFASPLTGIADASQSSMHNALHIYMNGTMSQVQGSANDPIFLLHHAF

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SEQ ID NO 5
ORIGIN
1 atcactgtag tagtagctgg aaagagaaat ctgtgactcc aattagccag ttcctgcaga
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121 ccagacctcc gctggccatt tccctagagc ctgtgtctcc tctaagaacc tgatggagaa
181 ggaatgctgt ccaccgtgga gcggggacag gagtccctgt ggccagcttt caggcagagg
241 ttcctgtcag aatatccttc tgtccaatgc accacttggg cctcaatttc ccttcacagg
301 ggtggatgac cgggagtcgt ggccttccgt cttttataat aggacctgcc agtgctctgg
361 caacttcatg ggattcaact gtggaaactg caagtttggc ttttggggac caaactgcac
421 agagagacga ctcttggtga gaagaaacat cttcgatttg agtgccccag agaaggacaa
481 atttttttgcc tacctcactt tagcaaagca taccatcagc tcagactatg tcatccccat
541 agggacctat ggccaaatga aaaatggatc aacacccatg tttaacgaca tcaatattta
601 tgacctcttt gtctggatgc attattatgt gtcaatggat gcactgcttg ggggatctga
661 aatctggaga gacattgatt ttgcccatga agcaccagct tttctgcctt ggcatagact
721 cttcttgttg cggtgggaac aagaaatcca gaagctgaca ggagatgaaa acttcactat
781 tccatattgg gactggcggg atgcagaaaa gtgtgacatt tgcacagatg agtacatggg
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961 cgagggacct ttacggcgta atcctggaaa ccatgacaaa tccagaaccc caaggctccc
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1081 taaagctgcc aatttcagct ttagaaatac actggaagga tttgctagtc cacttactgg

1141 gatagcggat gcctctcaaa gcagcatgca caatgccttg cacatctata tgaatggaac
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1441 agattcagac ccagactctt ttcaagacta cattaagtcc tatttggaac aagcgagtcg
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1561 agggcttgtg agcttgctgt gtcgtcacaa gagaaagcag cttcctgaag aaaagcagcc
1621 actcctcatg gagaaagagg attaccacag cttgtatcag agccatttat aaaaggctta
1681 ggcaatagag tagggccaaa aagcctgacc tcactctaac tcaaagtaat gtccaggttc
1741 ccagagaata tctgctggta tttttctgta aagaccattt gcaaaattgt aacctaatac
1801 aaagtgtagc cttcttccaa ctcaggtaga acacacctgt ctttgtcttg ctgttttcac
1861 tcagcccttt taacattttc ccctaagccc atatgtctaa ggaaaggatg ctatttggta
1921 atgaggaact gttatttgta tgtgaattaa agtgctctta tttt

Homo sapiens synovial sarcoma, X breakpoint 2 (SSX2), mRNA.
ACCESSION NM_003147
VERSION NM_003147.1 GI:10337582
SEQ ID NO 3

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EHAWTHRLRERKQLVIYEEISDPEEDDE"

SEQ ID NO 6
ORIGIN
1 ctctctttcg attcttccat actcagagta cgcacggtct gattttctct ttggattctt
61 ccaaaatcag agtcagactg ctcccggtgc catgaacgga gacgacgcct ttgcaaggag
121 acccacggtt ggtgctcaaa taccagagaa gatccaaaag gccttcgatg atattgccaa
181 atacttctct aaggaagagt gggaaaagat gaaagcctcg gagaaaatct tctatgtgta
241 tatgaagaga aagtatgagg ctatgactaa actaggtttc aaggccaccc tcccaccttt
301 catgtgtaat aaacgggccg aagacttcca ggggaatgat ttggataatg accctaaccg
361 tgggaatcag gttgaacgtc ctcagatgac tttcggcagg ctccagggaa tctccccgaa

421 gatcatgccc aagaagccag cagaggaagg aaatgattcg gaggaagtgc cagaagcatc
481 tggcccacaa aatgatggga aagagctgtg cccccggga aaaccaacta cctctgagaa
541 gattcacgag agatctggac ccaaaagggg ggaacatgcc tggacccaca gactgcgtga
601 gagaaaacag ctggtgattt atgaagagat cagcgaccct gaggaagatg acgagtaact
661 cccctcaggg atacgacaca tgcccatgat gagaagcaga acgtggtgac ctttcacgaa
721 catgggcatg gctgcggacc cctcgtcatc aggtgcatag caagtg

Homo sapiens folate hydrolase (prostate-specific membrane antigen) 1 (FOLH1), mRNA.
ACCESSION NM_004476
VERSION NM_004476.1 GI:4758397

SEQ ID No. 4
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FGLDSVELAHYDVLLSYPNKTHPNYISIINEDGNEIFNTSLFEPPPPGYENVSDIVPP

FSAFSPQGMPEGDLVYVNYARTEDFFKLERDMKINCSGKIVIARYGKVFRGNKVKNAQ

LAGAKGVILYSDPADYFAPGVKSYPDGWNLPGGGVQRGNILNLNGAGDPLTPGYPANE

YAYRRGIAEAVGLPSIPVHPIGYYDAQKLLEKMGGSAPPDSSWRGSLKVPYNVGPGFT

GNFSTQKVKMHIHSTNEVTRIYNVIGTLRGAVEPDRYVILGGHRDSWVFGGIDPQSGA

AVVHEIVRSFGTLKKEGWRPRRTILFASWDAEEFGLLGSTEWAEENSRLLQERGVAYI

NADSSIEGNYTLRVDCTPLMYSLVHNLTKELKSPDEGFEGKSLYESWTKKSPSPEFSG

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DPMFKYHLTVAQVRGGMVFELANSIVLPFDCRDYAVVLRKYADKIYSISMKHPQEMKT

YSVSFDSLFSAVKNFTEIASKFSERLQDFDKSNPIVLRMMNDQLMFLERAFIDPLGLP

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SEQ ID NO 7
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61 attggttcag tgcactctag aaacactgct gtggtggaga aactggaccc caggtctgga
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181 cccgccgtgg tggttggagg gcgcgcagta gagcagcagc acaggcgcgg gtcccgggag

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2401 gatattgaaa gcaaagtgga cccttccaag gcctggggag aagtgaagag acagatttat
2461 gttgcagcct tcacagtgca ggcagctgca gagactttga gtgaagtagc ctaagaggat
2521 tctttagaga atccgtattg aatttgtgtg gtatgtcact cagaaagaat cgtaatgggt
2581 atattgataa attttaaaat tggtatattt gaaataaagt tgaatattat atataaaaaa
2641 aaaaaaaaaa aaa

Human melanocyte-specific (pmel 17) gene, exons 2-5, and complete cds.
ACCESSION U20093
VERSION U20093.1 GI:1142634
SEQ ID NO 70

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SITGSLGPLLDGTATLRLVKRQVPLDCVLYRYGSFSVTLDIVQGIESAEILQAVPSGEGDAFELTV
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CPIGENSPLLSGQQV"

SEQ ID NO 80
ORIGIN
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481 ctatcatcca cacttgtgtt tacttctttc tacctgatca cctttctttt ggccgcccct
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661 ttgtagtcct accccatgga atgcctcatt aggacccctt ccctgtcccc ccatatcaca
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2701 cctcagtggg cagcaggtct gagtactctc atatgatgct gtgattttcc tggagttgac
2761 agaaacacct atatttcccc cagtcttccc tgggagacta ctattaactg aaataaa
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Homo sapiens kallikrein 3, (prostate specific antigen) (KLK3), mRNA.
ACCESSION NM_001648
VERSION NM_001648.1 GI:4502172
SEQ ID NO 78

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LRPGDDSSHDLMLLRLSEPAELTDAVKVMDLPTQEPALGTTCYASGWGSIEPEEFLTPKKLQCVDL
HVISNDVCAQVHPQKVTKFMLCAGRWTGGKSTCSGDSGGPLVCNGVLQGITSWGSEPCALPERPSL
YTKVVHYRKWIKDTIVANP"

SEQ ID NO 86
ORIGIN
1 agccccaagc ttaccacctg cacccggaga gctgtgtgtc accatgtggg tcccggttgt
61 cttcctcacc ctgtccgtga cgtggattgg tgctgcaccc ctcatcctgt ctcggattgt
121 gggaggctgg gagtgcgaga agcattccca accctggcag gtgcttgtgg cctctcgtgg
181 cagggcagtc tgcggcggtg ttctggtgca cccccagtgg gtcctcacag ctgcccactg
241 catcaggaac aaaagcgtga tcttgctggg tcggcacagc ctgtttcatc ctgaagacac
301 aggccaggta tttcaggtca gccacagctt cccacacccg ctctacgata tgagcctcct
361 gaagaatcga ttcctcaggc caggtgatga ctccagccac gacctcatgc tgctccgcct
421 gtcagagcct gccgagctca cggatgctgt gaaggtcatg gacctgccca cccaggagcc

481 agcactgggg accacctgct acgcctcagg ctggggcagc attgaaccag aggagttctt
541 gaccccaaag aaacttcagt gtgtggacct ccatgttatt tccaatgacg tgtgtgcgca
601 agttcaccct cagaaggtga ccaagttcat gctgtgtgct ggacgctgga caggggggcaa
661 aagcacctgc tcgggtgatt ctgggggccc acttgtctgt aatggtgtgc ttcaaggtat
721 cacgtcatgg ggcagtgaac catgtgccct gcccgaaagg ccttccctgt acaccaaggt
781 ggtgcattac cggaagtgga tcaaggacac catcgtggcc aacccctgag caccccctatc
841 aacccctat tgtagtaaac ttggaacctt ggaaatgacc aggccaagac tcaagcctcc
901 ccagttctac tgacctttgt ccttaggtgt gaggtccagg gttgctagga aaagaaatca
961 gcagacacag gtgtagacca gagtgtttct taaatggtgt aattttgtcc tctctgtgtc
1021 ctggggaata ctggccatgc ctggagacat atcactcaat ttctctgagg acacagatag
1081 gatggggtgt ctgtgttatt tgtggggtac agagatgaaa gaggggtggg atccacactg
1141 agagagtgga gagtgacatg tgctggacac tgtccatgaa gcactgagca gaagctggag
1201 gcacaacgca ccagacactc acagcaagga tggagctgaa aacataaccc actctgtcct
1261 ggaggcactg ggaagcctag agaaggctgt gagccaagga gggagggtct tcctttggca
1321 tgggatgggg atgaagtaag gagagggact ggacccctg gaagctgatt cactatgggg
1381 ggaggtgtat tgaagtcctc cagacaaccc tcagatttga tgatttccta gtagaactca
1441 cagaaataaa gagctgttat actgtg
//

Human autoimmunogenic cancer/testis antigen NY-ESO-1 mRNA, complete cds.
ACCESSION U87459
VERSION U87459.1 GI:1890098
SEQ ID NO 74

/translation="MQAEGRGTGGSTGDADGPGGPGIPDGPGGNAGGPGEAG
ATGGRGPRGAGAARASGPGGGAPRGPHGGAASGLNGCCRCGARGPESRLLEF
YLAMPFATPMEAELARRSLAQDAPPLPVPGVLLKEFTVSGNILTIRLTAADH
RQLQLSISSCLQQLSLLMWITQCFLPVFLAQPPSGQRR"

SEQ ID NO 84
ORIGIN
1 atcctcgtgg gccctgacct tctctctgag agccgggcag aggctccgga gccatgcagg
61 ccgaaggccg gggcacaggg ggttcgacgg gcgatgctga tggcccagga ggccctggca
121 ttcctgatgg cccagggggc aatgctggcg gcccaggaga ggcgggtgcc acgggcggca
181 gaggtccccg gggcgcaggg gcagcaaggg cctcggggcc gggaggaggc gccccgcggg

241 gtccgcatgg cggcgcggct tcagggctga atggatgctg cagatgcggg gccagggggc
301 cggagagccg cctgcttgag ttctacctcg ccatgccttt cgcgacaccc atggaagcag
361 agctggcccg caggagcctg gcccaggatg ccccaccgct tcccgtgcca ggggtgcttc
421 tgaaggagtt cactgtgtcc ggcaacatac tgactatccg actgactgct gcagaccacc
481 gccaactgca gctctccatc agctcctgtc tccagcagct ttccctgttg atgtggatca
541 cgcagtgctt tctgcccgtg tttttggctc agcctccctc agggcagagg cgctaagccc
601 agcctggcgc cccttcctag gtcatgcctc ctcccctagg gaatggtccc agcacgagtg
661 gccagttcat tgtgggggcc tgattgtttg tcgctggagg aggacggctt acatgtttgt
721 ttctgtagaa aataaaactg agctacgaaa aa
//

LAGE-1a protein [Homo sapiens].
ACCESSION CAA11116
PID g3255959
VERSION CAA11116.1 GI:3255959

SEQ ID NO 75
ORIGIN
1 mqaegrgtgg stgdadgpgg pgipdgpggn aggpgeagat ggrgprgaga arasgprgga
61 prgphggaas aqdgrcpcga rrpdsrllel hitmpfsspm eaelvrrils rdaaplprpg
121 avlkdftvsg nllfirltaa dhrqlqlsis sclqqlsllm witqcflpvf laqapsgqrr
181
//

LAGE-1b protein [Homo sapiens].
ACCESSION CAA11117
PID g3255960
VERSION CAA11117.1 GI:3255960

SEQ ID NO 76
ORIGIN
1 mqaegrgtgg stgdadgpgg pgipdgpggn aggpgeagat ggrgprgaga arasgprgga
61 prgphggaas aqdgrcpcga rrpdsrllel hitmpfsspm eaelvrrils rdaaplprpg
121 avlkdftvsg nllfmsvwdq dregagrmrv vgwglgsasp egqkardlrt pkhkvseqrp
181 gtpgppppeg aqgdgcrgva fnvmfsaphi
//

Human antigen (MAGE-1) gene, complete cds.
ACCESSION M77481
VERSION M77481.1 GI:416114
SEQ ID NO 71

/translation="MSLEQRSLHCKPEEALEAQQEALGLVCVQAATSSSSPL VLGTLEEVPTAGSTDPPQSPQGASAFPTTINFTRQRQPSEGSSSREEEGPST SCILESLFRAVITKKVADLVGFLLLKYRAREPVTKAEMLESVIKNYKHCFPE IFGKASESLQLVFGIDVKEADPTGHSYVLVTCLGLSYDGLLGDNQIMPKTGF LIIVLVMIAMEGGHAPEEEIWEELSVMEVYDGREHSAYGEPRKLLTQDLVQE KYLEYRQVPDSDPARYEFLWGPRALAETSYVKVLEYVIKVSARVRFFFPSLR EAALREEEEGV"

SEQ ID NO 81
ORIGIN
1 ggatccaggc cctgccagga aaaatataag ggccctgcgt gagaacagag ggggtcatcc
61 actgcatgag agtggggatg tcacagagtc cagcccaccc tcctggtagc actgagaagc
121 cagggctgtg cttgcggtct gcaccctgag ggcccgtgga ttcctcttcc tggagctcca
181 ggaaccaggc agtgaggcct tggtctgaga cagtatcctc aggtcacaga gcagaggatg
241 cacagggtgt gccagcagtg aatgtttgcc ctgaatgcac accaagggcc ccacctgcca
301 caggacacat aggactccac agagtctggc ctcacctccc tactgtcagt cctgtagaat
361 cgacctctgc tggccggctg taccctgagt accctctcac ttcctccttc aggttttcag
421 gggacaggcc aacccagagg acaggattcc ctggaggcca cagaggagca ccaaggagaa
481 gatctgtaag taggcctttg ttagagtctc caaggttcag ttctcagctg aggcctctca
541 cacactccct ctctccccag gcctgtgggt cttcattgcc cagctcctgc ccacactcct
601 gcctgctgcc ctgacgagag tcatcatgtc tcttgagcag aggagtctgc actgcaagcc
661 tgaggaagcc cttgaggccc aacaagaggc cctgggcctg gtgtgtgtgc aggctgccac
721 ctcctcctcc tctcctctgg tcctgggcac cctggaggag gtgcccactg ctgggtcaac
781 agatcctccc cagagtcctc agggagcctc cgcctttccc actaccatca acttcactcg
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901 tatcctggag tccttgttcc gagcagtaat cactaagaag gtggctgatt tggttggttt
961 tctgctcctc aaatatcgag ccagggagcc agtcacaaag gcagaaatgc tggagagtgt
1021 catcaaaaat tacaagcact gttttcctga gatcttcggc aaagcctctg agtccttgca
1081 gctggtcttt ggcattgacg tgaaggaagc agaccccacc ggccactcct atgtccttgt
1141 cacctgccta ggtctctcct atgatggcct gctgggtgat aatcagatca tgcccaagac
1201 aggcttcctg ataattgtcc tggtcatgat tgcaatggag ggcggccatg ctcctgagga
1261 ggaaatctgg gaggagctga gtgtgatgga ggtgtatgat gggagggagc acagtgccta
1321 tggggagccc aggaagctgc tcacccaaga tttggtgcag gaaaagtacc tggagtaccg

1381 gcaggtgccg gacagtgatc ccgcacgcta tgagttcctg tggggtccaa gggccctcgc
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1501 tttcttccca tccctgcgtg aagcagcttt gagagaggag gaagagggag tctgagcatg
1561 agttgcagcc aaggccagtg ggaggggac tgggccagtg caccttccag ggccgcgtcc
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1681 gtgttctcag tagtaggttt ctgttctatt gggtgacttg gagatttatc tttgttctct
1741 tttggaattg ttcaaatgtt tttttttaag ggatggttga atgaacttca gcatccaagt
1801 ttatgaatga cagcagtcac acagttctgt gtatatagtt taagggtaag agtcttgtgt
1861 tttattcaga ttgggaaatc cattctattt tgtgaattgg gataataaca gcagtggaat
1921 aagtacttag aaatgtgaaa aatgagcagt aaaatagatg agataaagaa ctaaagaaat
1981 taagagatag tcaattcttg ccttatacct cagtctattc tgtaaaattt ttaaagatat
2041 atgcatacct ggatttcctt ggcttctttg agaatgtaag agaaattaaa tctgaataaa
2101 gaattcttcc tgttcactgg ctcttttctt ctccatgcac tgagcatctg ctttttggaa
2161 ggccctgggt tagtagtgga gatgctaagg taagccagac tcatacccac ccatagggtc
2221 gtagagtcta ggagctgcag tcacgtaatc gaggtggcaa gatgtcctct aaagatgtag
2281 ggaaaagtga gagaggggtg agggtgtggg gctccgggtg agagtggtgg agtgtcaatg
2341 ccctgagctg gggcattttg ggctttggga aactgcagtt ccttctgggg gagctgattg
2401 taatgatctt gggtggatcc
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Human MAGE-2 gene exons 1-4, complete cds.
ACCESSION L18920
VERSION L18920.1 GI:436180
SEQ ID NO 72

/translation="MPLEQRSQHCKPEEGLEARGEALGLVGAQAPATEEQQTASSSSTLVEVT
LGEVPAADSPSPPHSPQGASSFSTTINYTLWRQSDEGSSNQEEEGPRMFPDLE
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VVEVVPISHLYILVTCLGLSYDGLLGDNQVMPKTGLLIIVLAIIAIEGDCAPEEKIWEELSML
EVFEGREDSVFAHPRKLLMQDLVQENYLEYRQVPGSDPACYEFLWGPRALIETSYVKVLHHTL
KIGGEPHISYPPLHERALREGEE"

SEQ ID NO 82
ORIGIN
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61 ccaccctcac cacatagtgg gaccacagaa tccagctcag cccctcttgt cagccctggt
121 acacactggc aatgatctca ccccgagcac acccctcccc ccaatgccac ttcgggccga

181 ctcagagtca gagacttggt ctgaggggag cagacacaat cggcagagga tggcggtcca
241 ggctcagtct ggcatccaag tcaggacctt gagggatgac caaaggcccc tcccaccccc
301 aactccccg accccaccag gatctacagc ctcaggatcc ccgtcccaat ccctacccct
361 acaccaacac catcttcatg cttaccccca cccccccatc cagatcccca tccgggcaga
421 atccggttcc acccttgccg tgaacccagg gaagtcacgg gcccggatgt gacgccactg
481 acttgcacat tggaggtcag aggacagcga gattctcgcc ctgagcaacg gcctgacgtc
541 ggcggaggga agcaggcgca ggctccgtga ggaggcaagg taagacgccg agggaggact
601 gaggcgggcc tcaccccaga cagagggccc ccaataatcc agcgctgcct ctgctgccgg
661 gcctggacca ccctgcaggg gaagacttct caggctcagt cgccaccacc tcaccccgcc
721 accccccgcc gctttaaccg cagggaactc tggcgtaaga gctttgtgtg accagggcag
781 ggctggttag aagtgctcag ggcccagact cagccaggaa tcaaggtcag gaccccaaga
841 ggggactgag ggcaacccac cccctaccct cactaccaat cccatccccc aacaccaacc
901 ccacccccat ccctcaaaca ccaaccccac ccccaaaccc cattcccatc tcctccccca
961 ccaccatcct ggcagaatcc ggctttgccc ctgcaatcaa cccacggaag ctccgggaat
1021 ggcggccaag cacgcggatc ctgacgttca catgtacggc taagggaggg aaggggttgg
1081 gtctcgtgag tatggccttt gggatgcaga ggaagggccc aggcctcctg gaagacagtg
1141 gagtccttag gggacccagc atgccaggac aggggggccca ctgtacccct gtctcaaact
1201 gagccacctt ttcattcagc cgagggaatc ctagggatgc agacccactt cagcaggggg
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1381 cccgtgctca ttgcaccttc agggtgacag agagttgagg gctgtggtct gagggctggg
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1561 ttgttcttag ctctggggga acctgatcag ggatggccct aagtgacaat ctcatttgta
1621 ccacaggcag gaggttgggg aaccctcagg gagataaggt gttggtgtaa agaggagctg
1681 tctgctcatt tcaggggggtt gggggttgag aaagggcagt ccctggcagg agtaaagatg
1741 agtaacccac aggaggccat cataacgttc accctagaac caaaggggtc agccctggac
1801 aacgcacgtg gggtaacag gatgtggccc ctcctcactt gtctttccag atctcaggga
1861 gttgatgacc ttgttttcag aaggtgactc aggtcaacac aggggcccca tctggtcgac

1921 agatgcagtg gttctaggat ctgccaagca tccaggtgga gagcctgagg taggattgag
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2041 ttacttcaga gaccctgggc agggctgtca gctgaagtcc ctccattatc ctgggatctt
2101 tgatgtcagg gaaggggagg ccttggtctg aaggggctgg agtcaggtca gtagagggag
2161 ggtctcaggc cctgccagga gtggacgtga ggaccaagcg gactcgtcac ccaggacacc
2221 tggactccaa tgaatttgga catctctcgt tgtccttcgc gggaggacct ggtcacgtat
2281 ggccagatgt gggtcccctc atatccttct gtaccatatc agggatgtga gttcttgaca
2341 tgagagattc tcaagccagc aaaagggtgg gattaggccc tacaaggaga aaggtgaggg
2401 ccctgagtga gcacagaggg gaccctccac ccaagtagag tggggacctc acggagtctg
2461 gccaaccctg ctgagacttc tgggaatccg tggctgtgct tgcagtctgc acactgaagg
2521 cccgtgcatt cctctcccag gaatcaggag ctccaggaac caggcagtga ggccttggtc
2581 tgagtcagtg tcctcaggtc acagagcaga ggggacgcag acagtgccaa cactgaaggt
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2701 tggcctcacc ctccctattc tcagtcctgc agcctgagca tgtgctggcc ggctgtaccc
2761 tgaggtgccc tcccacttcc tccttcaggt tctgaggggg acaggctgac aagtaggacc
2821 cgaggcactg gaggagcatt gaaggagaag atctgtaagt aagcctttgt cagagcctcc
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3001 tgcctcttga gcagaggagt cagcactgca agcctgaaga aggccttgag gcccgaggag
3061 aggccctggg cctggtgggt gcgcaggctc ctgctactga ggagcagcag accgcttctt
3121 cctcttctac tctagtggaa gttaccctgg gggaggtgcc tgctgccgac tcaccgagtc
3181 ctccccacag tcctcaggga gcctccagct tctcgactac catcaactac actctttgga
3241 gacaatccga tgagggctcc agcaaccaag aagaggaggg gccaagaatg tttcccgacc
3301 tggagtccga gttccaagca gcaatcagta ggaagatggt tgagttggtt cattttctgc
3361 tcctcaagta tcgagccagg gagccggtca caaaggcaga aatgctggag agtgtcctca
3421 gaaattgcca ggacttcttt cccgtgatct tcagcaaagc ctccgagtac ttgcagctgg
3481 tctttggcat cgaggtggtg gaagtggtcc ccatcagcca cttgtacatc cttgtcacct
3541 gcctgggcct ctcctacgat ggcctgctgg gcgacaatca ggtcatgccc aagacaggcc
3601 tcctgataat cgtcctggcc ataatcgcaa tagagggcga ctgtgcccct gaggagaaaa

3661 tctgggagga gctgagtatg ttggaggtgt ttgaggggag ggaggacagt gtcttcgcac
3721 atcccaggaa gctgctcatg caagatctgg tgcaggaaaa ctacctggag taccggcagg
3781 tgcccggcag tgatcctgca tgctacgagt tcctgtgggg tccaagggcc ctcattgaaa
3841 ccagctatgt gaaagtcctg caccatacac taaagatcgg tggagaacct cacatttcct
3901 acccacccct gcatgaacgg gctttgagag agggagaaga gtgagtctca gcacatgttg
3961 cagccagggc cagtgggagg gggtctgggc cagtgcacct tccagggccc catccattag
4021 cttccactgc ctcgtgtgat atgaggccca ttcctgcctc tttgaagaga gcagtcagca
4081 ttcttagcag tgagtttctg ttctgttgga tgactttgag atttatcttt ctttcctgtt
4141 ggaattgttc aaatgttcct tttaacaaat ggttggatga acttcagcat ccaagtttat
4201 gaatgacagt agtcacacat agtgctgttt atatagttta ggggtaagag tcctgttttt
4261 tattcagatt gggaaatcca ttccattttg tgagttgtca cataataaca gcagtggaat
4321 atgtatttgc ctatattgtg aacgaattag cagtaaaata catgatacaa ggaactcaaa
4381 agatagttaa ttcttgcctt atacctcagt ctattatgta aaattaaaaa tatgtgtatg
4441 tttttgcttc tttgagaatg caaaagaaat taaatctgaa taaattcttc ctgttcactg
4501 gctcatttct ttaccattca ctcagcatct gctctgtgga aggccctggt agtagtggg
//

Human MAGE-3 antigen (MAGE-3) gene, complete cds.
ACCESSION U03735
VERSION U03735.1 GI:468825
SEQ ID NO 73

/translation="MPLEQRSQHCKPEEGLEARGEALGLVGAQAPATEEQEAASSSSTLVEVTLGE
VPAAESPDPPQSPQGASSLPTTMNYPLWSQSYEDSSNQEEEGPSTFPDLESEFQAALSRKVAELVH
FLLLKYRAREPVTKAEMLGSVVGNWQYFFPVIFSKASSSLQLVFGIELMEVDPIGHLYIFATCLGL
SYDGLLGDNQIMPKAGLLIIVLAIIAREGDCAPEEKIWEELSVLEVFEGREDSILGDPKKLLTQHF
VQENYLEYRQVPGSDPACYEFLWGPRALVETSYVKVLHHMVKISGGPHISYPPLHEWVLREGEE"

SEQ ID NO 83
ORIGIN
1 acgcaggcag tgatgtcacc cagaccacac cccttccccc aatgccactt caggggtac
61 tcagagtcag agacttggtc tgaggggagc agaagcaatc tgcagaggat ggcggtccag
121 gctcagccag gcatcaactt caggaccctg agggatgacc gaaggccccg cccacccacc
181 cccaactccc ccgaccccac caggatctac agcctcagga cccccgtccc aatccttacc
241 ccttgcccca tcaccatctt catgcttacc tccacccccca tccgatcccc atccaggcag
301 aatccagttc cacccctgcc cggaacccag ggtagtaccg ttgccaggat gtgacgccac

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361 tgacttgcgc attggaggtc agaagaccgc gagattctcg ccctgagcaa cgagcgacgg
421 cctgacgtcg gcggagggaa gccggcccag gctcggtgag gaggcaaggt aagacgctga
481 gggaggactg aggcgggcct cacctcagac agagggcctc aaataatcca gtgctgcctc
541 tgctgccggg cctgggccac cccgcagggg aagacttcca ggctgggtcg ccactacctc
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661 cagggcaggg ctggttagaa gaggtcaggg cccacgctgt ggcaggaatc aaggtcagga
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1021 cagcatgcca ggacaggggg cccactgtac ccctgtctca aaccgaggca ccttttcatt
1081 cggctacggg aatcctaggg atgcagaccc acttcagcag gggggttgggg cccagccctg
1141 cgaggagtca tggggaggaa gaagagggag gactgagggg accttggagt ccagatcagt
1201 ggcaaccttg ggctggggga tgctgggcac agtggccaaa tgtgctctgt gctcattgcg
1261 ccttcagggt gaccagagag ttgagggctg tggtctgaag agtgggactt caggtcagca
1321 gagggaggaa tcccaggatc tgcagggccc aaggtgtacc cccaaggggc ccctatgtgg
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1921 gtctggccaa ccctcctgac agttctggga atccgtggct gcgtttgctg tctgcacatt
1981 gggggcccgt ggattcctct cccaggaatc aggagctcca ggaacaaggc agtgaggact
2041 tggtctgagg cagtgtcctc aggtcacaga gtagaggggg ctcagatagt gccaacggtg
```

2101 aaggtttgcc ttggattcaa accaagggcc ccacctgccc cagaacacat ggactccaga
2161 gcgcctggcc tcaccctcaa tactttcagt cctgcagcct cagcatgcgc tggccggatg
2221 taccctgagg tgccctctca cttcctcctt caggttctga ggggacaggc tgacctggag
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2341 cctccaaggt tccattcagt actcagctga ggtctctcac atgctccctc tctccccagg
2401 ccagtgggtc tccattgccc agctcctgcc cacactcccg cctgttgccc tgaccagagt
2461 catcatgcct cttgagcaga ggagtcagca ctgcaagcct gaagaaggcc ttgaggcccg
2521 aggagaggcc ctgggcctgg tgggtgcgca ggctcctgct actgaggagc aggaggctgc
2581 ctcctcctct tctactctag ttgaagtcac cctgggggag gtgcctgctg ccgagtcacc
2641 agatcctccc cagagtcctc agggagcctc cagcctcccc actaccatga actaccctct
2701 ctggagccaa tcctatgagg actccagcaa ccaagaagag gaggggccaa gcaccttccc
2761 tgacctggag tccgagttcc aagcagcact cagtaggaag gtggccgagt tggttcattt
2821 tctgctcctc aagtatcgag ccagggagcc ggtcacaaag gcagaaatgc tggggagtgt
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3001 cacctgcctg ggcctctcct acgatggcct gctgggtgac aatcagatca tgcccaaggc
3061 aggcctcctg ataatcgtcc tggccataat cgcaagagag ggcgactgtg cccctgagga
3121 gaaaatctgg gaggagctga gtgtgttaga ggtgtttgag gggagggaag acagtatctt
3181 gggggatccc aagaagctgc tcacccaaca tttcgtgcag gaaaactacc tggagtaccg
3241 gcaggtcccc ggcagtgatc ctgcatgtta tgaattcctg tggggtccaa gggccctcgt
3301 tgaaaccagc tatgtgaaag tcctgcacca tatggtaaag atcagtggag gacctcacat
3361 ttcctaccca cccctgcatg agtgggtttt gagagagggg gaagagtgag tctgagcacg
3421 agttgcagcc agggccagtg ggagggggtc tgggccagtg caccttccgg ggccgcatcc
3481 cttagtttcc actgcctcct gtgacgtgag gcccattctt cactctttga agcgagcagt
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3661 tttatgaatg acagtagtca cacatagtgc tgtttatata gtttaggagt aagagtcttg
3721 ttttttactc aaattgggaa atccattcca ttttgtgaat tgtgacataa taatagcagt
3781 ggtaaaagta tttgcttaaa attgtgagcg aattagcaat aacatacatg agataactca

3841 agaaatcaaa agatagttga ttcttgcctt gtacctcaat ctattctgta aaattaaaca
3901 aatatgcaaa ccaggatttc cttgacttct ttgagaatgc aagcgaaatt aaatctgaat
3961 aaataattct tcctcttcac tggctcgttt cttttccgtt cactcagcat ctgctctgtg
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4081 gctgtagagc ctaggacctg cagtcatata attaaggtgg tgagaagtcc tgtaagatgt
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4201 gtgc
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Homo sapiens prostate stem cell antigen (PSCA) mRNA, complete cds.
ACCESSION AF043498
VERSION AF043498.1 GI:2909843
SEQ ID NO 79

/translation="MKAVLLALLMAGLALQPGTALLCYSCKAQVSNEDCLQVENCTQLGEQCW
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LGLLLWGPGQL"

SEQ ID NO 87
ORIGIN
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121 gcctgcaggt ggagaactgc acccagctgg gggagcagtg ctggaccgcg cgcatccgcg
181 cagttggcct cctgaccgtc atcagcaaag gctgcagctt gaactgcgtg gatgactcac
241 aggactacta cgtgggcaag aagaacatca cgtgctgtga caccgacttg tgcaacgcca
301 gcggggccca tgccctgcag ccggctgccg ccatccttgc gctgctccct gcactcggcc
361 tgctgctctg gggacccggc cagctatagg ctctgggggg ccccgctgca gcccacactg
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481 cctggttcct gaggcacatc ctaacgcaag tttgaccatg tatgtttgca cccctttcc
541 ccnaaccctg accttcccat gggccttttc caggattccn accnggcaga tcagttttag
601 tganacanat ccgcntgcag atggcccctc caaccntttn tgttgntgtt tccatggccc
661 agcattttcc acccttaacc ctgtgttcag gcacttnttc ccccaggaag ccttccctgc
721 ccaccccatt tatgaattga gccaggtttg gtccgtggtg tcccccgcac ccagcagggg
781 acaggcaatc aggagggccc agtaaaggct gagatgaagt ggactgagta gaactggagg
841 acaagagttg acgtgagttc ctgggagttt ccagagatgg ggcctggagg cctggaggaa

901 ggggccaggc ctcacatttg tggggntccc gaatggcagc ctgagcacag cgtaggccct
961 taataaacac ctgttggata agccaaaaaa
//

GLANDULAR KALLIKREIN 1 PRECURSOR (TISSUE KALLIKREIN) (KIDNEY/PANCREAS/SALIVARY GLAND KALLIKREIN).
ACCESSION P06870
PID g125170
VERSION P06870 GI:125170

SEQ ID NO 105
ORIGIN
1 mwflvlclal slggtgaapp iqsrivggwe ceqhsqpwqa alyhfstfqc ggilvhrqwv
61 ltaahcisdn yqlwlgrhnl fddentaqfv hvsesfphpg fnmsllenht rqadedyshd
121 lmllrltepa dtitdavkvv elptqepevg stclasgwgs iepenfsfpd dlqcvdlkil
181 pndecekahv qkvtdfmlcv ghleggkdtc vgdsggplmc dgvlqgvtsw gyvpcgtpnk
241 psvavrvlsy vkwiedtiae ns
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ELASTASE 2A PRECURSOR.
ACCESSION P08217
PID g119255
VERSION P08217 GI:119255

SEQ ID NO 106
ORIGIN
1 mirtlllstl vagalscgdp typpyvtrvv ggeearpnsw pwqvslqyss ngkwyhtcgg
61 slianswvlt aahcisssrt yrvglgrhnl yvaesgslav svskivvhkd wnsnqiskgn
121 diallklanp vsltdkiqla clppagtilp nnypcyvtgw grlqtngavp dvlqqgrllv
181 vdyatcsssa wwgssvktsm icaggdgvis scngdsggpl ncqasdgrwq vhgivsfgsr
241 lgcnyyhkps vftrvsnyid winsviann
//

pancreatic elastase IIB [Homo sapiens].
ACCESSION NP_056933
PID g7705648
VERSION NP_056933.1 GI:7705648

SEQ ID NO 107
ORIGIN
1 mirtlllstl vagalscgvs tyapdmsrml ggeearpnsw pwqvslqyss ngqwyhtcgg
61 slianswvlt aahcisssri yrvmlgqhnl yvaesgslav svskivvhkd wnsnqvskgn
121 diallklanp vsltdkiqla clppagtilp nnypcyvtgw grlqtngalp ddlkqgrllv

181 vdyatcsssg wwgstvktnm icaggdgvic tcngdsggpl ncqasdgrwe vhgigsltsv
241 lgcnyyykps iftrvsnynd winsviann
//

PRAME Homo sapiens preferentially expressed antigen in melanoma (PRAME), mRNA.
ACCESSION NM_006115
VERSION NM_006115.1 GI:5174640
SEQ ID NO 77

/translation="MERRRLWGSIQSRYISMSVWTSPRRLVELAGQSLLKDEALAIAALELLPREL
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LQVLDLRKNSHQDFWTVWSGNRASLYSFPEPEAAQPMTKKRKVDGLSTEAEQPFIPVEVLVDLFLK
EGACDELFSYLIEKVKRKKNVLRLCCKKLKIFAMPMQDIKMILKMVQLDSIEDLEVTCTWKLPTLA
KFSPYLGQMINLRRLLLSHIHASSYISPEKEEQYIAQFTSQFLSLQCLQALYVDSLFFLRGRLDQL
LRHVMNPLETLSITNCRLSEGDVMHLSQSPSVSQLSVLSLSGVMLTDVSPEPLQALLERASATLQD
LVFDECGITDDQLLALLPSLSHCSQLTTLSFYGNSISISALQSLLQHLIGLSNLTHVLYPVPLESY
EDIHGTLHLERLAYLHARLRELLCELGRPSMVWLSANPCPHCGDRTFYDPEPILCPCFMPN"

SEQ ID NO 85
ORIGIN
1 gcttcagggt acagctcccc cgcagccaga agccgggcct gcagcccctc agcaccgctc
61 cgggacaccc cacccgcttc ccaggcgtga cctgtcaaca gcaacttcgc ggtgtggtga
121 actctctgag gaaaaaccat tttgattatt actctcagac gtgcgtggca acaagtgact
181 gagacctaga aatccaagcg ttggaggtcc tgaggccagc ctaagtcgct tcaaaatgga
241 acgaaggcgt ttgtggggtt ccattcagag ccgatacatc agcatgagtg tgtggacaag
301 cccacggaga cttgtggagc tggcagggca gagcctgctg aaggatgagg ccctggccat
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421 cgggagacac agccagaccc tgaaggcaat ggtgcaggcc tggcccttca cctgcctccc
481 tctgggagtg ctgatgaagg gacaacatct tcacctggag accttcaaag ctgtgcttga
541 tggacttgat gtgctccttg cccaggaggt tcgccccagg aggtggaaac ttcaagtgct
601 ggatttacgg aagaactctc atcaggactt ctggactgta tggtctggaa acagggccag
661 tctgtactca tttccagagc cagaagcagc tcagcccatg acaaagaagc gaaaagtaga
721 tggtttgagc acagaggcag agcagccctt cattccagta gaggtgctcg tagacctgtt
781 cctcaaggaa ggtgcctgtg atgaattgtt ctcctacctc attgagaaag tgaagcgaaa
841 gaaaaatgta ctacgcctgt gctgtaagaa gctgaagatt tttgcaatgc ccatgcagga
901 tatcaagatg atcctgaaaa tggtgcagct ggactctatt gaagatttgg aagtgacttg
961 tacctggaag ctacccacct tggcgaaatt ttctccttac ctgggccaga tgattaatct

1021 gcgtagactc ctcctctccc acatccatgc atcttcctac atttccccgg agaaggaaga
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1141 tgtggactct ttatttttcc ttagaggccg cctggatcag ttgctcaggc acgtgatgaa
1201 ccccttggaa accctctcaa taactaactg ccggctttcg gaaggggatg tgatgcatct
1261 gtcccagagt cccagcgtca gtcagctaag tgtcctgagt ctaagtgggg tcatgctgac
1321 cgatgtaagt cccgagcccc tccaagctct gctggagaga gcctctgcca ccctccagga
1381 cctggtcttt gatgagtgtg ggatcacgga tgatcagctc cttgccctcc tgccttccct
1441 gagccactgc tcccagctta caaccttaag cttctacggg aattccatct ccatatctgc
1501 cttgcagagt ctcctgcagc acctcatcgg gctgagcaat ctgacccacg tgctgtatcc
1561 tgtccccctg gagagttatg aggacatcca tggtaccctc cacctggaga ggcttgccta
1621 tctgcatgcc aggctcaggg agttgctgtg tgagttgggg cggcccagca tggtctggct
1681 tagtgccaac cctgtcctc actgtgggga cagaaccttc tatgacccgg agcccatcct
1741 gtgcccctgt ttcatgccta actagctggg tgcacatatc aaatgcttca ttctgcatac
1801 ttggacacta aagccaggat gtgcatgcat cttgaagcaa caaagcagcc acagtttcag
1861 acaaatgttc agtgtgagtg aggaaaacat gttcagtgag gaaaaaacat tcagacaaat
1921 gttcagtgag gaaaaaaagg ggaagttggg gataggcaga tgttgacttg aggagttaat
1981 gtgatctttg gggagataca tcttatagag ttagaaatag aatctgaatt tctaaaggga
2041 gattctggct tgggaagtac atgtaggagt taatccctgt gtagactgtt gtaaagaaac
2101 tgttgaaaat aaagagaagc aatgtgaagc aaaaaaaaaa aaaaaaaa

//

CEA Homo sapiens carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5), mRNA.

ACCESSION NM_004363

VERSION NM_004363.1 GI:11386170

SEQ ID NO 88

/translation="MESPSAPPHRWCIPWQRLLLTASLLTFWNPPTTAKLTIESTPFN
VAEGKEVLLLVHNLPQHLFGYSWYKGERVDGNRQIIGYVIGTQQATPGPAYSGREIIY
PNASLLIQNIIQNDTGFYTLHVIKSDLVNEEATGQFRVYPELPKPSISSNNSKPVEDK
DAVAFTCEPETQDATYLWWVNNQSLPVSPRLQLSNGNRTLTLFNVTRNDTASYKCETQ

NPVSARRSDSVILNVLYGPDAPTISPLNTSYRSGENLNLSCHAASNPPAQYSWFVNGT
FQQSTQELFIPNITVNNSGSYTCQAHNSDTGLNRTTVTTITVYAEPPKPFITSNNSNP
VEDEDAVALTCEPEIQNTTYLWWVNNQSLPVSPRLQLSNDNRTLTLLSVTRNDVGPYE
CGIQNELSVDHSDPVILNVLYGPDDPTISPSYTYYRPGVNLSLSCHAASNPPAQYSWL
IDGNIQQHTQELFISNITEKNSGLYTCQANNSASGHSRTTVKTITVSAELPKPSISSN
NSKPVEDKDAVAFTCEPEAQNTTYLWWVNGQSLPVSPRLQLSNGNRTLTLFNVTRNDA
RAYVCGIQNSVSANRSDPVTLDVLYGPDTPIISPPDSSYLSGANLNLSCHSASNPSPQ
YSWRINGIPQQHTQVLFIAKITPNNNGTYACFVSNLATGRNNSIVKSITVSASGTSPG
LSAGATVGIMIGVLVGVALI"

SEQ ID NO 89

ORIGIN

1 ctcagggcag agggaggaag gacagcagac cagacagtca cagcagcctt gacaaaacgt
61 tcctggaact caagctcttc tccacagagg aggacagagc agacagcaga gaccatggag
121 tctccctcgg cccctcccca cagatggtgc atcccctggc agaggctcct gctcacagcc
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301 tttggctaca gctggtacaa aggtgaaaga gtggatggca accgtcaaat tataggatat
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421 cccaatgcat ccctgctgat ccagaacatc atccagaatg acacaggatt ctacacccta
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601 gtggccttca cctgtgaacc tgagactcag gacgcaacct acctgtggtg ggtaaacaat
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781 gccaggcgca gtgattcagt catcctgaat gtcctctatg gcccggatgc ccccaccatt
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901 tctaacccac ctgcacagta ctcttggttt gtcaatggga ctttccagca atccacccaa
961 gagctcttta tccccaacat cactgtgaat aatagtggat cctatacgtg ccaagcccat
1021 aactcagaca ctggcctcaa taggaccaca gtcacgacga tcacagtcta tgcagagcca
1081 cccaaaccct tcatcaccag caacaactcc aaccccgtgg aggatgagga tgctgtagcc
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1201 ctcccggtca gtcccaggct gcagctgtcc aatgacaaca ggaccctcac tctactcagt
1261 gtcacaagga atgatgtagg accctatgag tgtggaatcc agaacgaatt aagtgttgac
1321 cacagcgacc cagtcatcct gaatgtcctc tatggcccag acgaccccac catttccccc
1381 tcatacacct attaccgtcc aggggtgaac ctcagcctct cctgccatgc agcctctaac
1441 ccacctgcac agtattcttg gctgattgat gggaacatcc agcaacacac acaagagctc
1501 tttatctcca acatcactga gaagaacagc ggactctata cctgccaggc caataactca
1561 gccagtggcc acagcaggac tacagtcaag acaatcacag tctctgcgga gctgcccaag
1621 ccctccatct ccagcaacaa ctccaaaccc gtggaggaca aggatgctgt ggccttcacc
1681 tgtgaacctg aggctcagaa cacaacctac ctgtggtggg taaatggtca gagcctccca
1741 gtcagtccca ggctgcagct gtccaatggc aacaggaccc tcactctatt caatgtcaca
1801 agaaatgacg caagagccta tgtatgtgga atccagaact cagtgagtgc aaaccgcagt
1861 gacccagtca ccctggatgt cctctatggg ccggacaccc ccatcatttc ccccccagac

1921 tcgtcttacc tttcgggagc gaacctcaac ctctcctgcc actcggcctc taacccatcc
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2041 gccaaaatca cgccaaataa taacgggacc tatgcctgtt ttgtctctaa cttggctact
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2281 taaagcattt gcaacagcta cagtctaaaa ttgcttcttt accaaggata tttacagaaa
2341 agactctgac cagagatcga gaccatccta gccaacatcg tgaaacccca tctctactaa
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2521 actgcactcc agtctggcaa cagagcaaga ctccatctca aaaagaaaag aaaagaagac
2581 tctgacctgt actcttgaat acaagtttct gataccactg cactgtctga gaatttccaa
2641 aactttaatg aactaactga cagcttcatg aaactgtcca ccaagatcaa gcagagaaaa
2701 taattaattt catgggacta aatgaactaa tgaggattgc tgattcttta aatgtcttgt
2761 ttcccagatt tcaggaaact ttttttcttt taagctatcc actcttacag caatttgata
2821 aaatatactt ttgtgaacaa aaattgagac atttacattt tctccctatg tggtcgctcc
2881 agacttggga aactattcat gaatatttat attgtatggt aatatagtta ttgcacaagt
2941 tcaataaaaa tctgctcttt gtataacaga aaaa
//

Her2/Neu Human tyrosine kinase-type receptor (HER2) mRNA, complete cds.

ACCESSION M11730
VERSION M11730.1 GI:183986
SEQ ID NO 90

/translation="MELAALCRWGLLLALLPPGAASTQVCTGTDMKLRLPASPETHLD
MLRHLYQGCQVVQGNLELTYLPTNASLSFLQDIQEVQGYVLIAHNQVRQVPLQRLRIV
RGTQLFEDNYALAVLDNGDPLNNTTPVTGASPGGLRELQLRSLTEILKGGVLIQRNPQ
LCYQDTILWKDIFHKNNQLALTLIDTNRSRACHPCSPMCKGSRCWGESSEDCQSLTRT
VCAGGCARCKGPLPTDCCHEQCAAGCTGPKHSDCLACLHFNHSGICELHCPALVTYNT
DTFESMPNPEGRYTFGASCVTACPYNYLSTDVGSCTLVCPLHNQEVTAEDGTQRCEKC
SKPCARVCYGLGMEHLREVRAVTSANIQEFAGCKKIFGSLAFLPESFDGDPASNTAPL
QPEQLQVFETLEEITGYLYISAWPDSLPDLSVFQNLQVIRGRILHNGAYSLTLQGLGI
SWLGLRSLRELGSGLALIHHNTHLCFVHTVPWDQLFRNPHQALLHTANRPEDECVGEG
LACHQLCARGHCWGPGPTQCVNCSQFLRGQECVEECRVLQGLPREYVNARHCLPCHPE
CQPQNGSVTCFGPEADQCVACAHYKDPPFCVARCPSGVKPDLSYMPIWKFPDEEGACQ
PCPINCTHSCVDLDDKGCPAEQRASPLTSIVSAVVGILLVVVLGVVFGILIKRRQQKI
RKYTMRRLLQETELVEPLTPSGAMPNQAQMRILKETELRKVKVLGSGAFGTVYKGIWI
PDGENVKIPVAIKVLRENTSPKANKEILDEAYVMAGVGSPYVSRLLGICLTSTVQLVT
QLMPYGCLLDHVRENRGRLGSQDLLNWCMQIAKGMSYLEDVRLVHRDLAARNVLVKSP
NHVKITDFGLARLLDIDETEYHADGGKVPIKWMALESILRRRFTHQSDVWSYGVTVWE
LMTFGAKPYDGIPAREIPDLLEKGERLPQPPICTIDVYMIMVKCWMIDSECRPRFREL
VSEFSRMARDPQRFVVIQNEDLGPASPLDSTFYRSLLEDDDMGDLVDAEEYLVPQQGF
FCPDPAPGAGGMVHHRHRSSSTRSGGGDLTLGLEPSEEEAPRSPLAPSEGAGSDVFDG
DLGMGAAKGLQSLPTHDPSPLQRYSEDPTVPLPSETDGYVAPLTCSPQPEYVNQPDVR
PQPPSPREGPLPAARPAGATLERAKTLSPGKNGVVKDVFAFGGAVENPEYLTPQGGAA
PQHPPPAFSPAFDNLYYWDQDPPERGAPPSTFKGTPTAENPEYLGLDVPV"

SEQ ID NO 91
ORIGIN Chromosome 17q21-q22.
1 aattctcgag ctcgtcgacc ggtcgacgag ctcgagggtc gacgagctcg agggcgcgcg
61 cccggccccc acccctcgca gcaccccgcg ccccgcgccc tcccagccgg gtccagccgg
121 agccatgggg ccggagccgc agtgagcacc atggagctgg cggccttgtg ccgctggggg
181 ctcctcctcg ccctcttgcc ccccggagcc gcgagcaccc aagtgtgcac cggcacagac
241 atgaagctgc ggctccctgc cagtcccgag acccacctgg acatgctccg ccacctctac

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961 ctggtcacct acaacacaga cacgtttgag tccatgccca atcccgaggg ccggtataca
1021 ttcggcgcca gctgtgtgac tgcctgtccc tacaactacc tttctacgga cgtgggatcc
1081 tgcaccctcg tctgccccct gcacaaccaa gaggtgacag cagaggatgg aacacagcgg
1141 tgtgagaagt gcagcaagcc ctgtgcccga gtgtgctatg gtctgggcat ggagcacttg
1201 cgagaggtga gggcagttac cagtgccaat atccaggagt ttgctggctg caagaagatc
1261 tttgggagcc tggcatttct gccggagagc tttgatgggg acccagcctc caacactgcc
1321 ccgctccagc cagagcagct ccaagtgttt gagactctgg aagagatcac aggttaccta
1381 tacatctcag catggccgga cagcctgcct gacctcagcg tcttccagaa cctgcaagta

1441 atccggggac gaattctgca caatggcgcc tactcgctga ccctgcaagg gctgggcatc
1501 agctggctgg ggctgcgctc actgagggaa ctgggcagtg gactggccct catccaccat
1561 aacacccacc tctgcttcgt gcacacggtg ccctgggacc agctctttcg gaacccgcac
1621 caagctctgc tccacactgc caaccggcca gaggacgagt gtgtgggcga gggcctggcc
1681 tgccaccagc tgtgcgcccg agggcactgc tggggtccag ggcccaccca gtgtgtcaac
1741 tgcagccagt tccttcgggg ccaggagtgc gtggaggaat gccgagtact gcaggggctc
1801 cccagggagt atgtgaatgc caggcactgt ttgccgtgcc accctgagtg tcagccccag
1861 aatggctcag tgacctgttt tggaccggag gctgaccagt gtgtggcctg tgcccactat
1921 aaggaccctc ccttctgcgt ggcccgctgc cccagcggtg tgaaacctga cctctcctac
1981 atgcccatct ggaagtttcc agatgaggag ggcgcatgcc agccttgccc catcaactgc
2041 acccactcct gtgtggacct ggatgacaag ggctgccccg ccgagcagag agccagccct
2101 ctgacgtcca tcgtctctgc ggtggttggc attctgctgg tcgtggtctt gggggtggtc
2161 tttgggatcc tcatcaagcg acggcagcag aagatccgga agtacacgat gcggagactg
2221 ctgcaggaaa cggagctggt ggagccgctg acacctagcg gagcgatgcc caaccaggcg
2281 cagatgcgga tcctgaaaga gacggagctg aggaaggtga aggtgcttgg atctggcgct
2341 tttggcacag tctacaaggg catctggatc cctgatgggg agaatgtgaa aattccagtg
2401 gccatcaaag tgttgaggga aaacacatcc cccaaagcca acaaagaaat cttagacgaa
2461 gcatacgtga tggctggtgt gggctcccca tatgtctccc gccttctggg catctgcctg
2521 acatccacgg tgcagctggt gacacagctt atgccctatg gctgcctctt agaccatgtc

2581 cgggaaaacc gcggacgcct gggctcccag gacctgctga actggtgtat gcagattgcc
2641 aaggggatga gctacctgga ggatgtgcgg ctcgtacaca gggacttggc cgctcggaac
2701 gtgctggtca agagtcccaa ccatgtcaaa attacagact tcgggctggc tcggctgctg
2761 gacattgacg agacagagta ccatgcagat gggggcaagg tgcccatcaa gtggatggcg
2821 ctggagtcca ttctccgccg gcggttcacc caccagagtg atgtgtggag ttatggtgtg
2881 actgtgtggg agctgatgac ttttggggcc aaaccttacg atgggatccc agcccgggag
2941 atccctgacc tgctggaaaa gggggagcgg ctgccccagc cccccatctg caccattgat
3001 gtctacatga tcatggtcaa atgttggatg attgactctg aatgtcggcc aagattccgg
3061 gagttggtgt ctgaattctc ccgcatggcc agggaccccc agcgctttgt ggtcatccag
3121 aatgaggact tgggcccagc cagtcccttg gacagcacct tctaccgctc actgctggag
3181 gacgatgaca tgggggacct ggtggatgct gaggagtatc tggtacccca gcagggcttc
3241 ttctgtccag accctgcccc gggcgctggg ggcatggtcc accacaggca ccgcagctca
3301 tctaccagga gtggcggtgg ggacctgaca ctagggctgg agccctctga agaggaggcc
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3421 ggaatggggg cagccaaggg gctgcaaagc ctccccacac atgaccccag ccctctacag
3481 cggtacagtg aggaccccac agtacccctg ccctctgaga ctgatggcta cgttgccccc
3541 ctgacctgca gcccccagcc tgaatatgtg aaccagccag atgttcggcc ccagcccccct
3601 tcgccccgag agggccctct gcctgctgcc cgacctgctg gtgccactct ggaaagggcc
3661 aagactctct ccccagggaa gaatggggtc gtcaaagacg tttttgcctt tgggggtgcc

3721 gtggagaacc ccgagtactt gacaccccag ggaggagctg cccctcagcc ccaccctcct
3781 cctgccttca gcccagcctt cgacaacctc tattactggg accaggaccc accagagcgg
3841 ggggctccac ccagcacctt caaagggaca cctacggcag agaacccaga gtacctgggt
3901 ctggacgtgc cagtgtgaac cagaaggcca agtccgcaga agccctgatg tgtcctcagg
3961 gagcagggaa ggcctgactt ctgctggcat caagaggtgg gagggccctc cgaccacttc
4021 caggggaacc tgccatgcca ggaacctgtc ctaaggaacc ttccttcctg cttgagttcc
4081 cagatggctg gaaggggtcc agcctcgttg gaagaggaac agcactgggg agtctttgtg
4141 gattctgagg ccctgcccaa tgagactcta gggtccagtg gatgccacag cccagcttgg
4201 ccctttcctt ccagatcctg ggtactgaaa gccttaggga agctggcctg agaggggaag
4261 cggccctaag ggagtgtcta agaacaaaag cgacccattc agagactgtc cctgaaacct
4321 agtactgccc cccatgagga aggaacagca atggtgtcag tatccaggct ttgtacagag
4381 tgcttttctg tttagttttt actttttttg ttttgttttt ttaaagacga aataaagacc
4441 caggggagaa tgggtgttgt atggggaggc aagtgtgggg ggtccttctc cacacccact
4501 ttgtccattt gcaaatatat tttggaaaac
//

H.sapiens mRNA for SCP1 protein.
ACCESSION X95654
VERSION X95654.1 GI:1212982
SEQ ID NO 92

/translation="MEKQKPFALFVPPRSSSSQVSAVKPQTLGGDSTFFKSFNKCTED
DLEFPFAKTNLSKNGENIDSDPALQKVNFLPVLEQVGNSDCHYQEGLKDSDLENSEGL
SRVFSKLYKEAEKIKKWKVSTEAELRQKESKLQENRKIIEAQRKAIQELQFGNEKVSL
KLEEGIQENKDLIKENNATRHLCNLLKETCARSAEKTKKYEYEREETRQVYMDLNNNI

EKMITAHGELRVQAENSRLEMHFKLKEDYEKIQHLEQEYKKEINDKEKQVSLLLIQIT
EKENKMKDLTFLLEESRDKVNQLEEKTKLQSENLKQSIEKQHHLTKELEDIKVSLQRS
VSTQKALEEDLQIATKTICQLTEEKETQMEESNKARAAHSFVVTEFETTVCSLEELLR
TEQQRLEKNEDQLKILTMELQKKSSELEEMTKLTNNKEVELEELKKVLGEKETLLYEN
KQFEKIAEELKGTEQELIGLLQAREKEVHDLEIQLTAITTSEQYYSKEVKDLKTELEN
EKLKNTELTSHCNKLSLENKELTQETSDMTLELKNQQEDINNNKKQEERMLKQIENLQ
ETETQLRNELEYVREELKQKRDEVKCKLDKSEENCNNLRKQVENKNKYIEELQQENKA
LKKKGTAESKQLNVYEIKVNKLELELESAKQKFGEITDTYQKEIEDKKISEENLLEEV
EKAKVIADEAVKLQKEIDKRCQHKIAEMVALMEKHKHQYDKIIEERDSELGLYKSKEQ
EQSSLRASLEIELSNLKAELLSVKKQLEIEREEKEKLKREAKENTATLKEKKDKKTQT
FLLETPEIYWKLDSKAVPSQTVSRNFTSVDHGISKDKRDYLWTSAKNTLSTPLPKAYT
VKTPTKPKLQQRENLNIPIEESKKKRKMAFEFDINSDSSETTDLLSMVSEEETLKTLY
RNNNPPASHLCVKTPKKAPSSLTTPGPTLKFGAIRKMREDRWAVIAKMDRKKKLKEAE
KLFV"

SEQ ID NO 93
ORIGIN
1 gccctcatag accgtttgtt gtagttcgcg tgggaacagc aacccacggt ttcccgatag
61 ttcttcaaag atatttacaa ccgtaacaga gaaaatggaa aagcaaaagc cctttgcatt
121 gttcgtacca ccgagatcaa gcagcagtca ggtgtctgcg gtgaaacctc agaccctggg
181 aggcgattcc actttcttca agagtttcaa caaatgtact gaagatgatt tggagtttcc
241 atttgcaaag actaatctct ccaaaaatgg ggaaaacatt gattcagatc ctgctttaca
301 aaaagttaat ttcttgcccg tgcttgagca ggttggtaat tctgactgtc actatcagga
361 aggactaaaa gactctgatt tggagaattc agagggattg agcagagtgt tttcaaaact
421 gtataaggag gctgaaaaga taaaaaaatg gaaagtaagt acagaagctg aactgagaca
481 gaaagaaagt aagttgcaag aaaacagaaa gataattgaa gcacagcgaa aagccattca
541 ggaactgcaa tttggaaatg aaaaagtaag tttgaaatta gaagaaggaa tacaagaaaa
601 taaagattta ataaaagaga ataatgccac aaggcattta tgtaatctac tcaaagaaac

661 ctgtgctaga tctgcagaaa agacaaagaa atatgaatat gaacgggaag aaaccaggca
721 agtttatatg gatctaaata ataacattga gaaaatgata acagctcatg gggaacttcg
781 tgtgcaagct gagaattcca gactggaaat gcattttaag ttaaaggaag attatgaaaa
841 aatccaacac cttgaacaag aatacaagaa ggaaataaat gacaaggaaa agcaggtatc
901 actactattg atccaaatca ctgagaaaga aaataaaatg aaagatttaa catttctgct
961 agaggaatcc agagataaag ttaatcaatt agaggaaaag acaaaattac agagtgaaaa
1021 cttaaaacaa tcaattgaga aacagcatca tttgactaaa gaactagaag atattaaagt
1081 gtcattacaa agaagtgtga gtactcaaaa ggctttagag gaagatttac agatagcaac
1141 aaaaacaatt tgtcagctaa ctgaagaaaa agaaactcaa atggaagaat ctaataaagc
1201 tagagctgct cattcgtttg tggttactga atttgaaact actgtctgca gcttggaaga
1261 attattgaga acagaacagc aaagattgga aaaaaatgaa gatcaattga aaatacttac
1321 catggagctt caaaagaaat caagtgagct ggaagagatg actaagctta caaataacaa
1381 agaagtagaa cttgaagaat tgaaaaaagt cttgggagaa aaggaaacac ttttatatga
1441 aaataaacaa tttgagaaga ttgctgaaga attaaaagga acagaacaag aactaattgg
1501 tcttctccaa gccagagaga aagaagtaca tgatttggaa atacagttaa ctgccattac
1561 cacaagtgaa cagtattatt caaaagaggt taaagatcta aaaactgagc ttgaaaacga
1621 gaagcttaag aatactgaat taacttcaca ctgcaacaag ctttcactag aaaacaaaga
1681 gctcacacag gaaacaagtg atatgaccct agaactcaag aatcagcaag aagatattaa
1741 taataacaaa aagcaagaag aaaggatgtt gaaacaaata gaaaatcttc aagaaacaga

1801 aacccaatta agaaatgaac tagaatatgt gagagaagag ctaaaacaga aaagagatga
1861 agttaaatgt aaattggaca agagtgaaga aaattgtaac aatttaagga aacaagttga
1921 aaataaaaac aagtatattg aagaacttca gcaggagaat aaggccttga aaaaaaaagg
1981 tacagcagaa agcaagcaac tgaatgttta tgagataaag gtcaataaat tagagttaga
2041 actagaaagt gccaaacaga aatttggaga aatcacagac acctatcaga aagaaattga
2101 ggacaaaaag atatcagaag aaaatctttt ggaagaggtt gagaaagcaa aagtaatagc
2161 tgatgaagca gtaaaattac agaaagaaat tgataagcga tgtcaacata aaatagctga
2221 aatggtagca cttatggaaa aacataagca ccaatatgat aagatcattg aagaaagaga
2281 ctcagaatta ggactttata agagcaaaga acaagaacag tcatcactga gagcatcttt
2341 ggagattgaa ctatccaatc tcaaagctga acttttgtct gttaagaagc aacttgaaat
2401 agaaagagaa gagaaggaaa aactcaaaag agaggcaaaa gaaaacacag ctactcttaa
2461 agaaaaaaaa gacaagaaaa cacaaacatt tttattggaa acacctgaaa tttattggaa
2521 attggattct aaagcagttc cttcacaaac tgtatctcga aatttcacat cagttgatca
2581 tggcatatcc aaagataaaa gagactatct gtggacatct gccaaaaata ctttatctac
2641 accattgcca aaggcatata cagtgaagac accaacaaaa ccaaaactac agcaaagaga
2701 aaacttgaat atacccattg aagaaagtaa aaaaaagaga aaaatggcct ttgaatttga
2761 tattaattca gatagttcag aaactactga tcttttgagc atggtttcag aagaagagac
2821 attgaaaaca ctgtatagga acaataatcc accagcttct catctttgtg tcaaaacacc
2881 aaaaaaggcc ccttcatctc taacaacccc tggacctaca ctgaagtttg gagctataag

2941 aaaaatgcgg gaggaccgtt gggctgtaat tgctaaaatg gatagaaaaa aaaaactaaa
3001 agaagctgaa aagttatttg tttaatttca gagaatcagt gtagttaagg agcctaataa
3061 cgtgaaactt atagttaata ttttgttctt atttgccaga gccacatttt atctggaagt
3121 tgagacttaa aaaatacttg catgaatgat ttgtgtttct ttatattttt agcctaaatg
3181 ttaactacat attgtctgga aacctgtcat tgtattcaga taattagatg attatatatt
3241 gttgttactt tttcttgtat tcatgaaaac tgtttttact aagttttcaa atttgtaaag
3301 ttagcctttg aatgctagga atgcattatt gagggtcatt ctttattctt tactattaaa
3361 atattttgga tgcaaaaaaa aaaaaaaaaa aaa
//

Homo sapiens synovial sarcoma, X breakpoint 4 (SSX4), mRNA.
ACCESSION NM_005636
VERSION NM_005636.1 GI:5032122
SEQ ID NO 94

/translation="MNGDDAFARRPRDDAQISEKLRKAFDDIAKYFSKKEWEKMKSSEKIVY
VYMKLNYEVMTKLGFKVTLPPFMRSKRAADFHGNDFGNDRNHRNQVERPQMTFG
SLQRIFPKIMPKKPAEEENGLKEVPEASGPQNDGKQLCPPGNPSTLEKINKTSGPKRG
KHAWTHRLRERKQLVVYEEISDPEEDDE"

SEQ ID NO 95
ORIGIN
1 atgaacggag acgacgcctt tgcaaggaga cccagggatg atgctcaaat atcagagaag
61 ttacgaaagg ccttcgatga tattgccaaa tacttctcta agaaagagtg ggaaaagatg
121 aaatcctcgg agaaaatcgt ctatgtgtat atgaagctaa actatgaggt catgactaaa
181 ctaggtttca aggtcaccct cccacctttc atgcgtagta aacgggctgc agacttccac

241 gggaatgatt ttggtaacga tcgaaaccac aggaatcagg ttgaacgtcc tcagatgact

301 ttcggcagcc tccagagaat cttcccgaag atcatgccca agaagccagc agaggaagaa

361 aatggtttga aggaagtgcc agaggcatct ggcccacaaa atgatgggaa acagctgtgc

421 cccccgggaa atccaagtac cttggagaag attaacaaga catctggacc caaaaggggg

481 aaacatgcct ggacccacag actgcgtgag agaaagcagc tggtggttta tgaagagatc

541 agcgaccctg aggaagatga cgagtaactc ccctcg

U19142. Human GAGE-1 prot...[gi:914898]

LOCUS HSU19142 646 bp mRNA linear

DEFINITION Human GAGE-1 protein mRNA, complete cds.

ACCESSION U19142

VERSION U19142.1 GI:914898

SEQ ID No. 96

/translation="MSWRGRSTYRPRPRRYVEPPEMIGPMRPEQFSDEVEPATPEEGE

PATQRQDPAAAQEGEDEGASAGQGPKPEADSQEQGHPQTGCECEDGPDGQEMDPPNPE
EVKTPEEEMRSHYVAQTGILWLLMNNCFLNLSPRKP"

SEQ ID NO. 97

1 ctgccgtccg gactcttttt cctctactga gattcatctg tgtgaaatat gagttggcga

61 ggaagatcga cctatcggcc tagaccaaga cgctacgtag agcctcctga aatgattggg

121 cctatgcggc ccgagcagtt cagtgatgaa gtggaaccag caacacctga agaaggggaa

181 ccagcaactc aacgtcagga tcctgcagct gctcaggagg gagaggatga gggagcatct

241 gcaggtcaag ggccgaagcc tgaagctgat agccaggaac agggtcaccc acagactggg

301 tgtgagtgtg aagatggtcc tgatgggcag gagatggacc cgccaaatcc agaggaggtg

361 aaaacgcctg aagaagagat gaggtctcac tatgttgccc agactgggat tctctggctt
421 ttaatgaaca attgcttctt aaatctttcc ccacggaaac cttgagtgac tgaaatatca
481 aatggcgaga gaccgtttag ttcctatcat ctgtggcatg tgaagggcaa tcacagtgtt
541 aaaagaagac atgctgaaat gttgcaggct gctcctatgt tggaaaattc ttcattgaag
601 ttctcccaat aaagctttac agccttctgc aaagaaaaaa aaaaaa
//

NM_001168. Homo sapiens bacu...[gi:4502144]
LOCUS BIRC5 1619 bp mRNA linear
DEFINITION Homo sapiens baculoviral IAP repeat-containing 5 (survivin) (BIRC5), mRNA.
ACCESSION NM_001168
VERSION NM_001168.1 GI:4502144

SEQ ID NO. 98
/translation="MGAPTLPPAWQPFLKDHRISTFKNWPFLEGCACTPERMAEAGFI

HCPTENEPDLAQCFFCFKELEGWEPDDDPIEEHKKHSSGCAFLSVKKQFEELTLGEFL
KLDRERAKNKIAKETNNKKKEFEETAKKVRRAIEQLAAMD"

SEQ ID NO. 99
1 ccgccagatt tgaatcgcgg gacccgttgg cagaggtggc ggcggcggca tgggtgcccc
61 gacgttgccc cctgcctggc agccctttct caaggaccac cgcatctcta cattcaagaa
121 ctggcccttc ttggagggct gcgcctgcac cccggagcgg atggccgagg ctggcttcat
181 ccactgcccc actgagaacg agccagactt ggcccagtgt ttcttctgct tcaaggagct
241 ggaaggctgg gagccagatg acgaccccat agaggaacat aaaaagcatt cgtccggttg
301 cgctttcctt tctgtcaaga agcagtttga agaattaacc cttggtgaat ttttgaaact
361 ggacagagaa agagccaaga acaaaattgc aaaggaaacc aacaataaga agaaagaatt

421 tgaggaaact gcgaagaaag tgcgccgtgc catcgagcag ctggctgcca tggattgagg
481 cctctggccg gagctgcctg gtcccagagt ggctgcacca cttccagggt ttattccctg
541 gtgccaccag ccttcctgtg ggccccttag caatgtctta ggaaaggaga tcaacatttt
601 caaattagat gtttcaactg tgctcctgtt ttgtcttgaa agtggcacca gaggtgcttc
661 tgcctgtgca gcgggtgctg ctggtaacag tggctgcttc tctctctctc tctctttttt
721 gggggctcat ttttgctgtt ttgattcccg ggcttaccag gtgagaagtg agggaggaag
781 aaggcagtgt cccttttgct agagctgaca gctttgttcg cgtgggcaga gccttccaca
841 gtgaatgtgt ctggacctca tgttgttgag gctgtcacag tcctgagtgt ggacttggca
901 ggtgcctgtt gaatctgagc tgcaggttcc ttatctgtca cacctgtgcc tcctcagagg
961 acagtttttt tgttgttgtg tttttttgtt tttttttttt ggtagatgca tgacttgtgt
1021 gtgatgagag aatggagaca gagtccctgg ctcctctact gtttaacaac atggctttct
1081 tattttgttt gaattgttaa ttcacagaat agcacaaact acaattaaaa ctaagcacaa
1141 agccattcta agtcattggg gaaacggggt gaacttcagg tggatgagga gacagaatag
1201 agtgatagga agcgtctggc agatactcct tttgccactg ctgtgtgatt agacaggccc
1261 agtgagccgc ggggcacatg ctggccgctc ctccctcaga aaaaggcagt ggcctaaatc
1321 ctttttaaat gacttggctc gatgctgtgg gggactggct gggctgctgc aggccgtgtg
1381 tctgtcagcc caaccttcac atctgtcacg ttctccacac gggggagaga cgcagtccgc
1441 ccaggtcccc gctttctttg gaggcagcag ctcccgcagg gctgaagtct ggcgtaagat
1501 gatggatttg attcgccctc ctccctgtca tagagctgca gggtggattg ttacagcttc

1561 gctggaaacc tctggaggtc atctcggctg ttcctgagaa ataaaaagcc tgtcatttc
//

U06452. Human melanoma an...[gi:476131]
LOCUS HSU06452 1524 bp mRNA linear
DEFINITION Human melanoma antigen recognized by T-cells (MART-1) mRNA.
ACCESSION U06452
VERSION U06452.1 GI:476131

SEQ ID NO.100
/translation="MPREDAHFIYGYPKKGHGHSYTTAEEAAGIGILTVILGVLLLIG

CWYCRRRNGYRALMDKSLHVGTQCALTRRCPQEGFDHRDSKVSLQEKNCEPVVPNAPP
AYEKLSAEQSPPPYSP"

SEQ ID NO. 101
1 agcagacaga ggactctcat taaggaaggt gtcctgtgcc ctgaccctac aagatgccaa
61 gagaagatgc tcacttcatc tatggttacc ccaagaaggg gcacggccac tcttacacca
121 cggctgaaga ggccgctggg atcggcatcc tgacagtgat cctgggagtc ttactgctca
181 tcggctgttg gtattgtaga agacgaaatg gatacagagc cttgatggat aaaagtcttc
241 atgttggcac tcaatgtgcc ttaacaagaa gatgcccaca agaagggttt gatcatcggg
301 acagcaaagt gtctcttcaa gagaaaaact gtgaacctgt ggttcccaat gctccacctg
361 cttatgagaa actctctgca gaacagtcac caccacctta ttcaccttaa gagccagcga
421 gacacctgag acatgctgaa attatttctc tcacactttt gcttgaattt aatacagaca
481 tctaatgttc tcctttggaa tggtgtagga aaaatgcaag ccatctctaa taataagtca
541 gtgttaaaat tttagtaggt ccgctagcag tactaatcat gtgaggaaat gatgagaaat

601 attaaattgg gaaaactcca tcaataaatg ttgcaatgca tgatactatc tgtgccagag
661 gtaatgttag taaatccatg gtgttatttt ctgagagaca gaattcaagt gggtattctg
721 gggccatcca atttctcttt acttgaaatt tggctaataa caaactagtc aggttttcga
781 accttgaccg acatgaactg tacacagaat tgttccagta ctatggagtg ctcacaaagg
841 atacttttac aggttaagac aaagggttga ctggcctatt tatctgatca agaacatgtc
901 agcaatgtct ctttgtgctc taaaattcta ttatactaca ataatatatt gtaaagatcc
961 tatagctctt ttttttgag atggagtttc gcttttgttg cccaggctgg agtgcaatgg
1021 cgcgatcttg gctcaccata acctccgcct cccaggttca agcaattctc ctgccttagc
1081 ctcctgagta gctgggatta caggcgtgcg ccactatgcc tgactaattt tgtagtttta
1141 gtagagacgg ggtttctcca tgttggtcag gctggtctca aactcctgac ctcaggtgat
1201 ctgcccgcct cagcctccca aagtgctgga attacaggcg tgagccacca cgcctggctg
1261 gatcctatat cttaggtaag acatataacg cagtctaatt acatttcact tcaaggctca
1321 atgctattct aactaatgac aagtattttc tactaaacca gaaattggta gaaggattta
1381 aataagtaaa agctactatg tactgcctta gtgctgatgc ctgtgtactg ccttaaatgt
1441 acctatggca atttagctct cttgggttcc caaatccctc tcacaagaat gtgcagaaga
1501 aatcataaag gatcagagat tctg
//

U19180. Human B melanoma ...[gi:726039]
LOCUS HSU19180 1004 bp mRNA linear
DEFINITION Human B melanoma antigen (BAGE) mRNA, complete cds.
ACCESSION U19180
VERSION U19180.1 GI:726039

SEQ IS NO. 102

/translation="MAARAVFLALSAQLLQARLMKEESPVVSWRLEPEDGTALCFIF"

SEQ ID NO. 103

1 cgccaattta gggtctccgg tatctcccgc tgagctgctc tgttcccggc ttagaggacc
61 aggagaaggg ggagctggag gctggagcct gtaacaccgt ggctcgtctc actctggatg
121 gtggtggcaa cagagatggc agcgcagctg gagtgttagg agggcggcct gagcggtagg
181 agtggggctg gagcagtaag atggcggcca gagcggtttt tctggcattg tctgcccagc
241 tgctccaagc caggctgatg aaggaggagt cccctgtggt gagctggagg ttggagcctg
301 aagacggcac agctctgtgc ttcatcttct gaggttgtgg cagccacggt gatggagacg
361 gcagctcaac aggagcaata ggaggagatg gagtttcact gtgtcagcca ggatggtctc
421 gatctcctga cctcgtgatc cgcccgcctt ggccttccaa agtgccgaga ttacagcgat
481 gtgcattttg taagcacttt ggagccacta tcaaatgctg tgaagagaaa tgtacccaga
541 tgtatcatta tccttgtgct gcaggagccg gctcctttca ggatttcagt cacatcttcc
601 tgctttgtcc agaacacatt gaccaagctc ctgaaagatg taagtttact acgcatagac
661 ttttaaactt caaccaatgt atttactgaa aataacaaat gttgtaaatt ccctgagtgt
721 tattctactt gtattaaaag gtaataatac ataatcatta aaatctgagg gatcattgcc
781 agagattgtt ggggagggaa atgttatcaa cggtttcatt gaaattaaat ccaaaaagtt
841 atttcctcag aaaaatcaaa taaagtttgc atgtttttta ttcttaaaac attttaaaaa
901 ccactgtaga atgatgtaaa tagggactgt gcagtatttc tgacatatac tataaaatta
961 ttaaaaagtc aatcagtatt caacatcttt tacactaaaa agcc

//

The teachings and embodiments disclosed in any of the publications, including patents, patent publications and non-patent publications, disclosed herein are contemplated as supporting principals and embodiments related to and useful in connection with the present invention.

The invention illustratively described herein suitably may be practiced in the absence of any element or elements, limitation or limitations which is not specifically disclosed herein. The terms and expressions which have been employed are used as terms of description and not of limitation, and there is no intention that in the use of such terms and expressions indicates the exclusion of equivalents of the features shown and described or portions thereof. It is recognized that various modifications are possible within the scope of the invention claimed. Thus, it should be understood that although the present invention has been specifically disclosed by preferred embodiments and optional features, modification and variation of the concepts herein disclosed may be resorted to by those skilled in the art, and that such modifications and variations are considered to be within the scope of the embodiments of this invention.

WHAT IS CLAIMED IS:

1. A polypeptide, comprising a component selected from the group consisting of:

(i) a polypeptide epitope having the sequence as disclosed in TABLE 1B;

(ii) an epitope cluster comprising the polypeptide of (i);

(iii) a polypeptide having substantial similarity to (i) or (ii);

(iv) a polypeptide having functional similarity to any of (i) through (iii); and

(v) a nucleic acid encoding the polypeptide of any of (i) through (iv).

2. The polypeptide of claim 1, wherein the polypeptide is immunologically active.

3. The polypeptide of claim 1, wherein the polypeptide is less than about 30 amino acids in length.

4. The polypeptide of claim 1, wherein the polypeptide is 8 to 10 amino acids in length.

5. The polypeptide of claim 1, wherein the substantial or functional similarity comprises addition of at least one amino acid.

6. The polypeptide of claim 5, wherein the at least one additional amino acid is at an N-terminus of the polypeptide.

7. The polypeptide of claim 1, wherein the substantial or functional similarity comprises a substitution of at least one amino acid.

8. The polypeptide of claim 1, the polypeptide having affinity to an HLA-A2 molecule.

9. The polypeptide of claim 8, wherein the affinity is determined by an assay of binding.

10. The polypeptide of claim 8, wherein the affinity is determined by an assay of restriction of epitope recognition.

11. The polypeptide of claim 8, wherein the affinity is determined by a prediction algorithm.

12. The polypeptide of claim 1, the polypeptide having affinity to an HLA-B7 or HLA-B51 molecule.

13. The polypeptide of claim 1, wherein the polypeptide is a housekeeping epitope.

14. The polypeptide of claim 1, wherein the polypeptide corresponds to an epitope displayed on a tumor cell.

15. The polypeptide of claim 1, wherein the polypeptide corresponds to an epitope displayed on a neovasculature cell.

16. The polypeptide of claim 1, wherein the polypeptide is an immune epitope.

17. The polypeptide of claim 1, wherein the polypeptide is encoded by a nucleic acid.

18. A composition comprising the polypeptide of claim 1 and a pharmaceutically acceptable adjuvant, carrier, diluent, or excipient.

19. The composition of claim 18, where the adjuvant is a polynucleotide.

20. The composition of claim 19 wherein the polynucleotide comprises a dinucleotide.

21. The composition of claim 20 wherein the dinucleotide is CpG.

22. The composition of claim 18, wherein the adjuvant is encoded by a polynucleotide.

23. The composition of claim 18 wherein the adjuvant is a cytokine.

24. The composition of claim 23 wherein the cytokine is GM-CSF.

25. The composition of claim 18 further comprising a professional antigen-presenting cell (pAPC).

26. The composition of claim 25, wherein the pAPC is a dendritic cell.

27. The composition of claim 18, further comprising a second epitope.

28. The composition of claim 27, wherein the second epitope is a polypeptide.

29. The composition of claim 27, wherein the second epitope is a nucleic acid.

30. The composition of claim 27, wherein the second epitope is a housekeeping epitope.

31. The composition of claim 27, wherein the second epitope is an immune epitope.

32. A composition comprising the nucleic acid of claim 1 and a pharmaceutically acceptable adjuvant, carrier, diluent, or excipient.

33. A recombinant construct comprising the nucleic acid of Claim 1.

34. The construct of claim 33, further comprising a plasmid, a viral vector, a bacterial vector, or an artificial chromosome.

35. The construct of claim 33, further comprising a sequence encoding at least one feature selected from the group consisting of a second epitope, an IRES, an ISS, an NIS, and ubiquitin.

36. A purified antibody that specifically binds to the polypeptide of claim 1.

37. A purified antibody that specifically binds to a peptide-MHC protein complex comprising the polypeptide of claim 1.

38. The antibody of claim 36 or claim 37, wherein the antibody is a monoclonal antibody.

39. A multimeric MHC-peptide complex comprising the polypeptide of claim 1.

40. An isolated T cell expressing a T cell receptor specific for an MHC-peptide complex, the complex comprising the polypeptide of claim 1.

41. The T cell of claim 40, produced by an *in vitro* immunization.

42. The T cell of claim 40, isolated from an immunized animal.

43. A T cell clone comprising the T cell of claim 40.

44. A polyclonal population of T cells comprising the T cell of claim 40.

45. A pharmaceutical composition comprising the T cell of claim 40 and a pharmaceutically acceptable adjuvant, carrier, diluent, or excipient.

46. An isolated protein molecule comprising the binding domain of a T cell receptor specific for an MHC-peptide complex, the complex comprising the epitope of claim 1.

47. The protein of claim 46, wherein the protein is multivalent.

48. An isolated nucleic acid encoding the protein of claim 46.

49. A recombinant construct comprising the nucleic acid of claim 48.

50. A host cell expressing a recombinant construct, the construct comprising the nucleic acid of claim 1, or the construct encoding a protein molecule comprising the binding domain of a T cell receptor specific for an MHC-peptide complex.

51. The host cell of claim 50, wherein the host cell is a dendritic cell, macrophage, tumor cell, or tumor-derived cell.

52. The host cell of claim 50, wherein the host cell is a bacterium, fungus, or protozoan.

53. A composition comprising the host cell of claim 50 and a pharmaceutically acceptable adjuvant, carrier, diluent, or excipient.

54. A composition comprising at least one component selected from the group consisting of the epitope of claim 1; the composition of claim 18, 32, or 45, the construct of claim 33; the T cell of claim 40, a host cell expressing a recombinant construct comprising a nucleic acid encoding a T cell receptor binding domain specific for an MHC-peptide complex and a composition comprising the same, and a host cell expressing a recombinant construct comprising the nucleic acid of claim 1 and a composition comprising the same.

55. A method of treating an animal, comprising:

administering to an animal the composition of claim 54.

56. The method of claim 55, wherein the administering step comprises a mode of delivery selected from the group consisting of transdermal, intranodal, perinodal, oral, intravenous, intradermal, intramuscular, intraperitoneal, mucosal, aerosol inhalation, and instillation.

57. The method of claim 55, further comprising a step of assaying to determine a characteristic indicative of a state of a target cell or target cells.

58. The method of claim 57, comprising a first assaying step and a second assaying step, wherein the first assaying step precedes the administering step, and wherein the second assaying step follows the administering step.

59. The method of claim 58, further comprising a step of comparing the characteristic determined in the first assaying step with the characteristic determined in the second assaying step to obtain a result.

60. The method of claim 59, wherein the result is selected from the group consisting of: evidence of an immune response, a diminution in number of target cells, a loss of mass or size of a tumor comprising target cells, a decrease in number or concentration of an intracellular parasite infecting target cells.

61. A method of evaluating immunogenicity of an immunogenic composition, comprising:

administering to an animal the composition of claim 54; and

evaluating immunogenicity based on a characteristic of the animal.

62. The method of claim 61, wherein the animal is MHC-transgenic.

63. A method of evaluating immunogenicity , comprising:

in vitro stimulation of a T cell with the composition of claim 54; and

evaluating immunogenicity based on a characteristic of the T cell.

64. The method of claim 63, wherein the stimulation is a primary stimulation.

65. A method of making a passive/adoptive immunotherapeutic, comprising:

combining the T cell of claim 40, or a host cell expressing a recombinant construct comprising a nucleic acid encoding a T cell receptor binding domain specific for an MHC-peptide complex, or a host cell expressing a recombinant construct comprising the nucleic acid of claim 1 with a pharmaceutically acceptable adjuvant, carrier, diluent, or excipient.

66. A method of determining specific T cell frequency comprising the step of contacting T cells with a MHC-peptide complex comprising the polypeptide of claim 1.

67. The method of claim 66, wherein the contacting step comprises at least one feature selected from the group consisting of immunization, restimulation, detection, and enumeration.

68. The method of Claim 66, further comprising ELISPOT analysis, limiting dilution analysis, flow cytometry, in situ hybridization, the polymerase chain reaction or any combination thereof.

69. A method of evaluating immunologic response, comprising the method of claim 66 carried out prior to and subsequent to an immunization step.

70. A method of evaluating immunologic response, comprising:

determining frequency, cytokine production, or cytolytic activity of T cells, prior to and subsequent to a step of stimulation with MHC-peptide complexes comprising the polypeptide of claim 1.

71. A method of diagnosing a disease comprising:

contacting a subject tissue with at least one component selected from the group consisting of the T cell of claim 40, the host cell of claim 50, the antibody of claim 36, and the protein of claim 46; and

diagnosing the disease based on a characteristic of the tissue or of the component.

72. The method of claim 71, wherein the contacting step takes place *in vivo*.

73. The method of claim 71, wherein the contacting step takes place *in vitro*.

74. A method of making a vaccine, comprising:

combining at least one component selected from the group consisting of the polypeptide of claim 1; the composition of claim 18, 32, 45, or 53; the construct of claim 33; the T cell of claim 40, and the host cell of claim 50, with a pharmaceutically acceptable adjuvant, carrier, diluent, or excipient.

75. A computer readable medium having recorded thereon the sequence of any one of SEQ ID NOS: 108-610, in a machine having a hardware or software that calculates the physical, biochemical, immunologic, or molecular genetic properties of a molecule embodying said sequence.

76. A method of treating an animal comprising combining the method of claim 55 combined with at least one mode of treatment selected from the group of radiation therapy, chemotherapy, biochemotherapy, and surgery.

77. An isolated polypeptide comprising an epitope cluster from a target-associated antigen having the sequence as disclosed in Tables 68-73, wherein the amino acid sequence consists of not more than about 80% of the amino acid sequence of the antigen.

78. A vaccine or immunotherapeutic product comprising the polypeptide of claim 77.

79. An isolated polynucleotide encoding the polypeptide of claim 77.

80. A vaccine or immunotherapeutic product comprising the polynucleotide of claim 79.

81. The polynucleotide of claim 79 or 80, wherein the polynucleotide is DNA.

82. The polynucleotide of claim 79 or 80, wherein the polynucleotide is RNA.

FIG. 1A

		1 … 50
CTAG_HUMAN NY-ESO	(1)	MQAEGRGTGGSTGDADGPGGPGIPDGPGGNAGGPGEAGATGGRGPRGAGA
AAD05202 - CAG-3	(1)	MQAEGRGTGGSTGDADGPGGPGIPDGPGGNAGGPGEAGATGGRGPRGAGA
CAA11044 -LAGE-1a	(1)	MQAEGQGTGGSTGDADGPGGPGIPDGPGGNAGGPGEAGATGGRGPRGAGA
CAA10194 - LAGE-1s	(1)	MQAEGQGTGGSTGDADGPGGPGIPDGPGGNAGGPGEAGATGGRGPRGAGA
CAA11043 - LAGE-1b	(1)	MQAEGQGTGGSTGDADGPGGPGIPDGPGGNAGGPGEAGATGGRGPRGAGA
CAA10196 - LAGE-1L	(1)	MQAEGQGTGGSTGDADGPGGPGIPDGPGGNAGGPGEAGATGGRGPRGAGA
AAH02883 CT-2	(1)	MQAEGRGTGGSTGDADGPGGPGIPDGPGGNAGGPGEAGATGGRGPRGAGA
Consensus	(1)	MQAEGRGTGGSTGDADGPGGPGIPDGPGGNAGGPGEAGATGGRGPRGAGA

		51 … 100
CTAG_HUMAN NY-ESO	(51)	ARASGPGGGAPRGPHGGAASGLNGCCRCGARGPESRLLEFYLAMPFATPM
AAD05202 - CAG-3	(51)	ARASGPGGGAPRGPHGGAASGLNGCCRCGARGPESRLLEFYLAMPFATPM
CAA11044 -LAGE-1a	(51)	ARASGPRGGAPRGPHGGAASAQDGRCPCGARRPDSRLLQLHITMPFSSPM
CAA10194 - LAGE-1s	(51)	ARASGPRGGAPRGPHGGAASAQDGRCPCGARRPDSRLLQLHITMPFSSPM
CAA11043 - LAGE-1b	(51)	ARASGPRGGAPRGPHGGAASAQDGRCPCGARRPDSRLLQLHITMPFSSPM
CAA10196 - LAGE-1L	(51)	ARASGPRGGAPRGPHGGAASAQDGRCPCGARRPDSRLLQLHITMPFSSPM
AAH02833 CT-2	(51)	ARASGPRGGAPRGPHGGAASAQDGRCPCGARRPDSRLLQLHITMPFSSPM
Consensus	(51)	ARASGPRGGAPRGPHGGAASAQDGRCPCGARRPDSRLLQLHITMPFSSPM

FIG. 1B

		101 150
CTAG_HUMAN NY-ESO	(101)	EAELARRSLAQDAPPLPVPGVLLKEFTVSGNILTIRLTAADHRQLQLSIS
AAD05202 - CAG-3	(101)	EAELARRSLAQDAPPLPVPGVLLKEFTVSGNILTIRLTAADHRQLQLSIS
CAA11044 -LAGE-1a	(101)	EAELVRRILSRDAAPLPRPGAVLKDFTVSGNLLFIRLTAADHRQLQLSIS
CAA10194 - LAGE-1s	(101)	EAELVRRILSRDAAPLPRPGAVLKDFTVSGNLLFIRLTAADHRQLQLSIS
CAA11043 - LAGE-1b	(101)	EAELVRRILSRDAAPLPRPGAVLKDFTVSGNLLFMSVRDQDREGAGRMRV
CAA10196 - LAGE-1L	(101)	EAELVRRILSRDAAPLPRPGAVLKDFTVSGNLLFMSVRDQDREGAGRMRV
AAH02833 CT-2	(101)	EAELVRRILSRDAAPLPRPGAVLKDFTVSGNLLFMSVRDQDREGAGRMRV
Consensus	(101)	EAELVRRILSRDAAPLPRPGAVLKDFTVSGNLLFIRLTAADHRQLQLSIS
		151 200
CTAG_HUMAN NY-ESO	(151)	SCLQQLSLLMWITQCFLPVFLAQPPSGQRR--------------------
AAD05202 - CAG-3	(151)	SCLQQLSLLMWITQCFLPVFLAQPPSGQRR--------------------
CAA11044 -LAGE-1a	(151)	SCLQQLSLLMWITQCFLPVFLAQPPSGQRR--------------------
CAA10194 - LAGE-1s	(151)	SCLQQLSLLMWITQCFLPVFLAQPPSGQRR--------------------
CAA11043 - LAGE-1b	(151)	VGWGLGSASPEGQKARDLRTPKHKVSEQRPGTPGPPPPEGAQGDGCRGVA
CAA10196 - LAGE-1L	(151)	VGWGLGSASPEGQKARDLRTPKHKVSEQRPGTPGPPPPEGAQGDGCRGVA
AAH02833 CT-2	(151)	VGWGLGSASPEGQKARDLRTPKHKVSEQRPGTPGPPPPEGAQGDGCRGVA
Consensus	(151)	SCLQQLSLLMWITQCFLPVFLAQ PSGQRR--------------------

FIG. 1C

		201
CTAG_HUMAN NY-ESO	(181)	----------
AAD05202 - CAG-3	(181)	----------
CAA11044 -LAGE-1a	(181)	----------
CAA10194 - LAGE-1s	(181)	----------
CAA11043 - LAGE-1b	(201)	FNVMFSAPHI
CAA10196 - LAGE-1L	(201)	FNVMFSAPHI
AAH02833 CT-2	(201)	FNVMFSAPHI
Consensus	(201)	

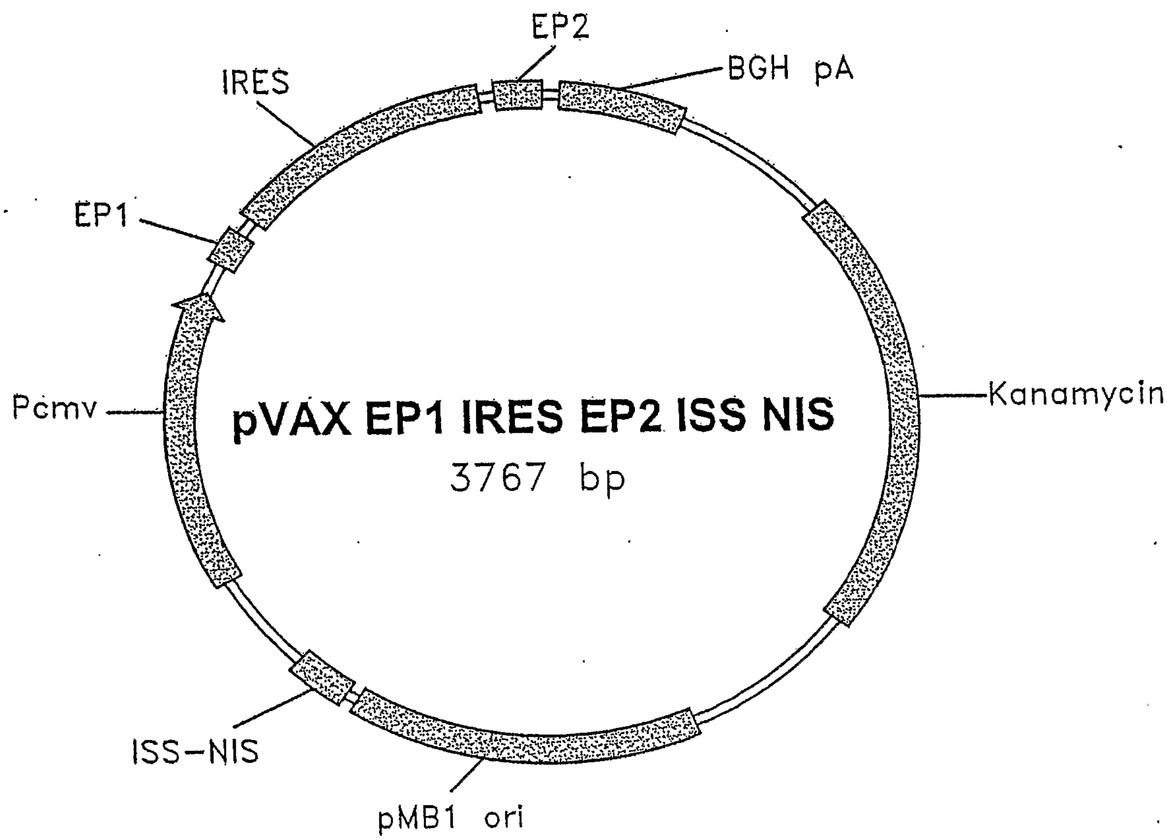

EP2
BGH pA
IRES
EP1
Kanamycin
Pcmv
pVAX EP1 IRES EP2 ISS NIS
3767 bp
ISS-NIS
pMB1 ori

FIG. 2

FIG. 3A

FACscan Analysis of Binding Assay to Determine the Binding Ability of Tyrosinase 208-216 Peptide to MHC Class 1

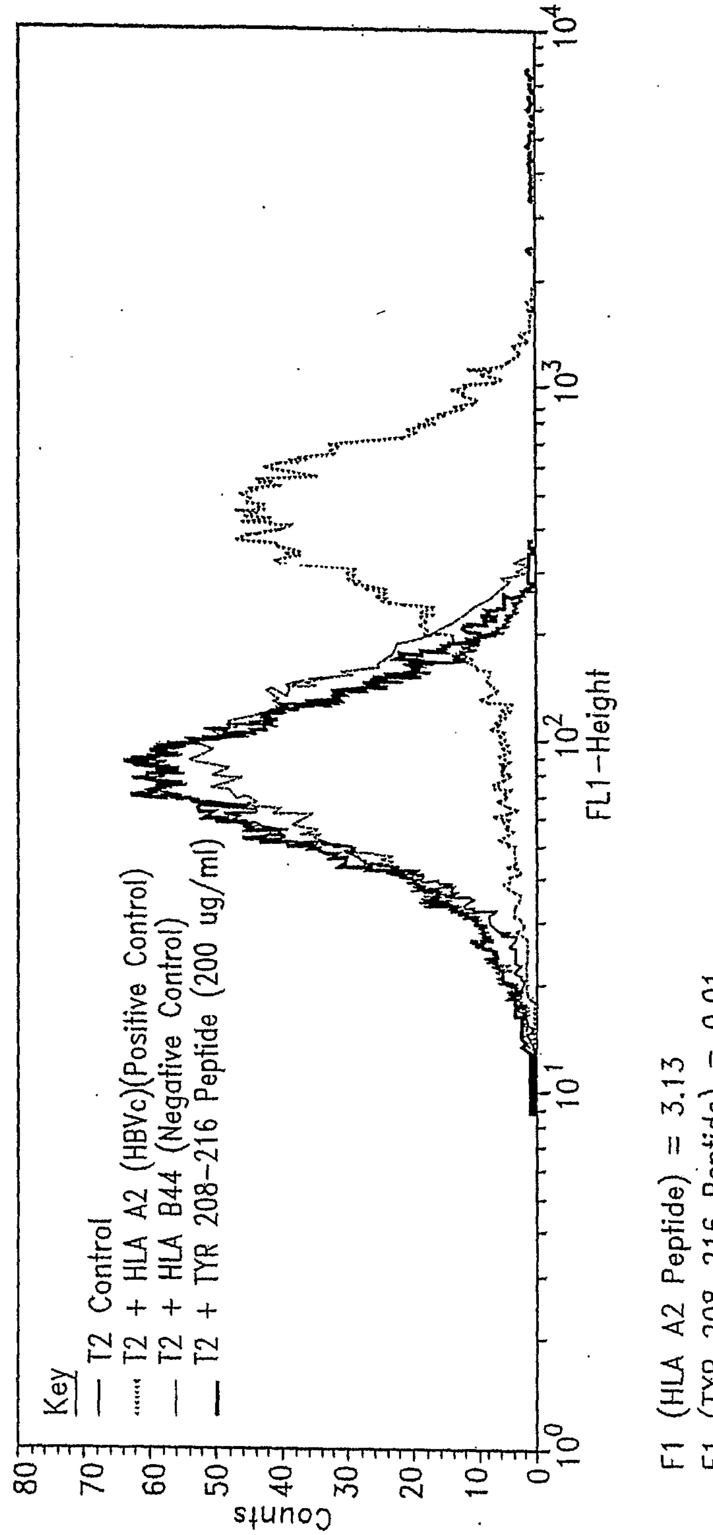
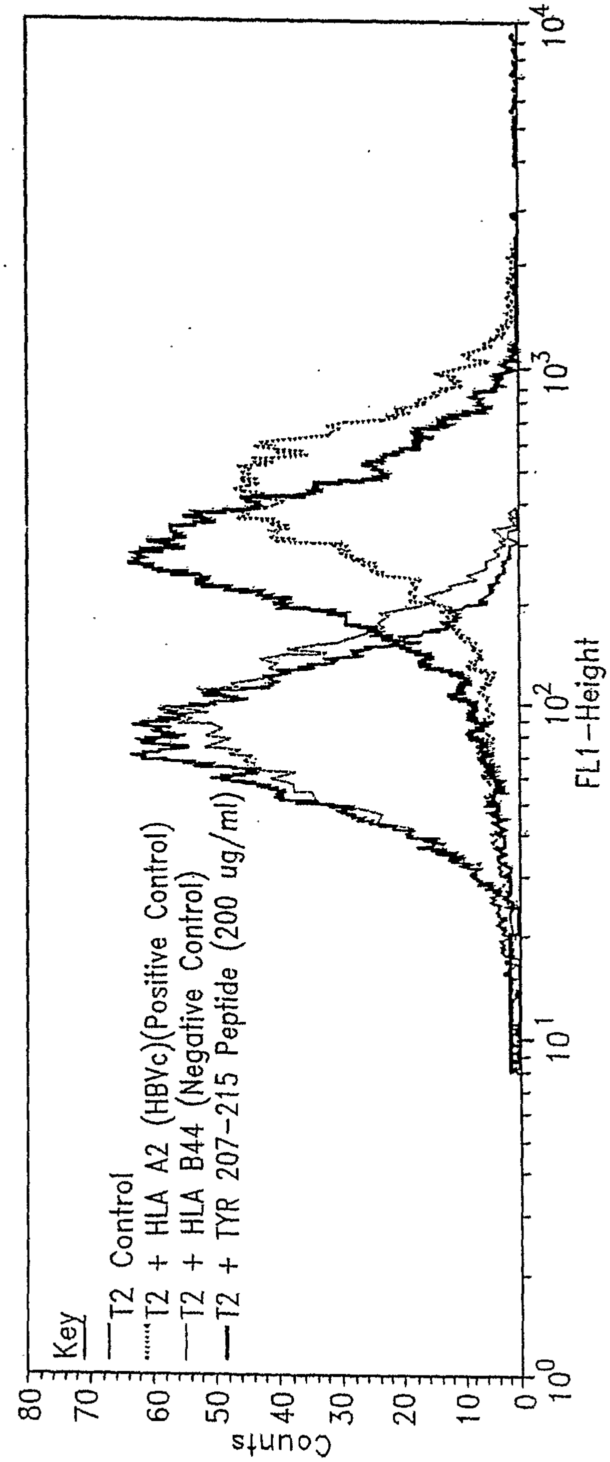


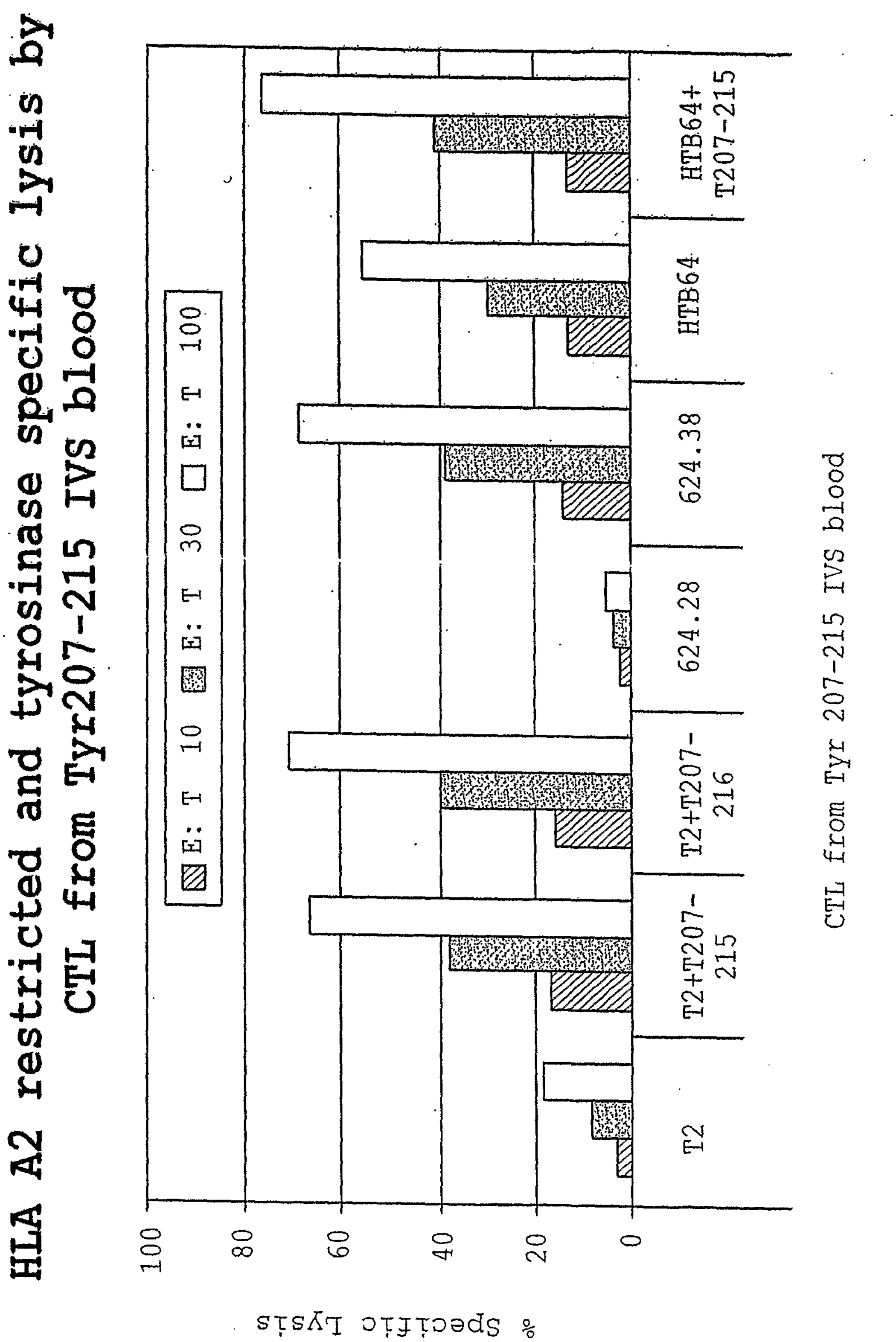
FIG. 3B

FACscan Analysis of Binding Assay to Determine the Binding Ability of Tyrosinase 207-215 Peptide to MHC Class 1



F1 (HLA A2 Peptide) = 3.13
F1 (TYR 207–215 Peptide) = 2.00

FIG. 3C


HLA A2 restricted and tyrosinase specific lysis by CTL from Tyr207-215 IVS blood
E: T 10
E: T 30
E: T 100
% Specific Lysis
100
80
60
40
20
0
T2
T2+T207-215
T2+T207-216
624.28
624.38
HTB64
HTB64+T207-215
CTL from Tyr 207-215 IVS blood

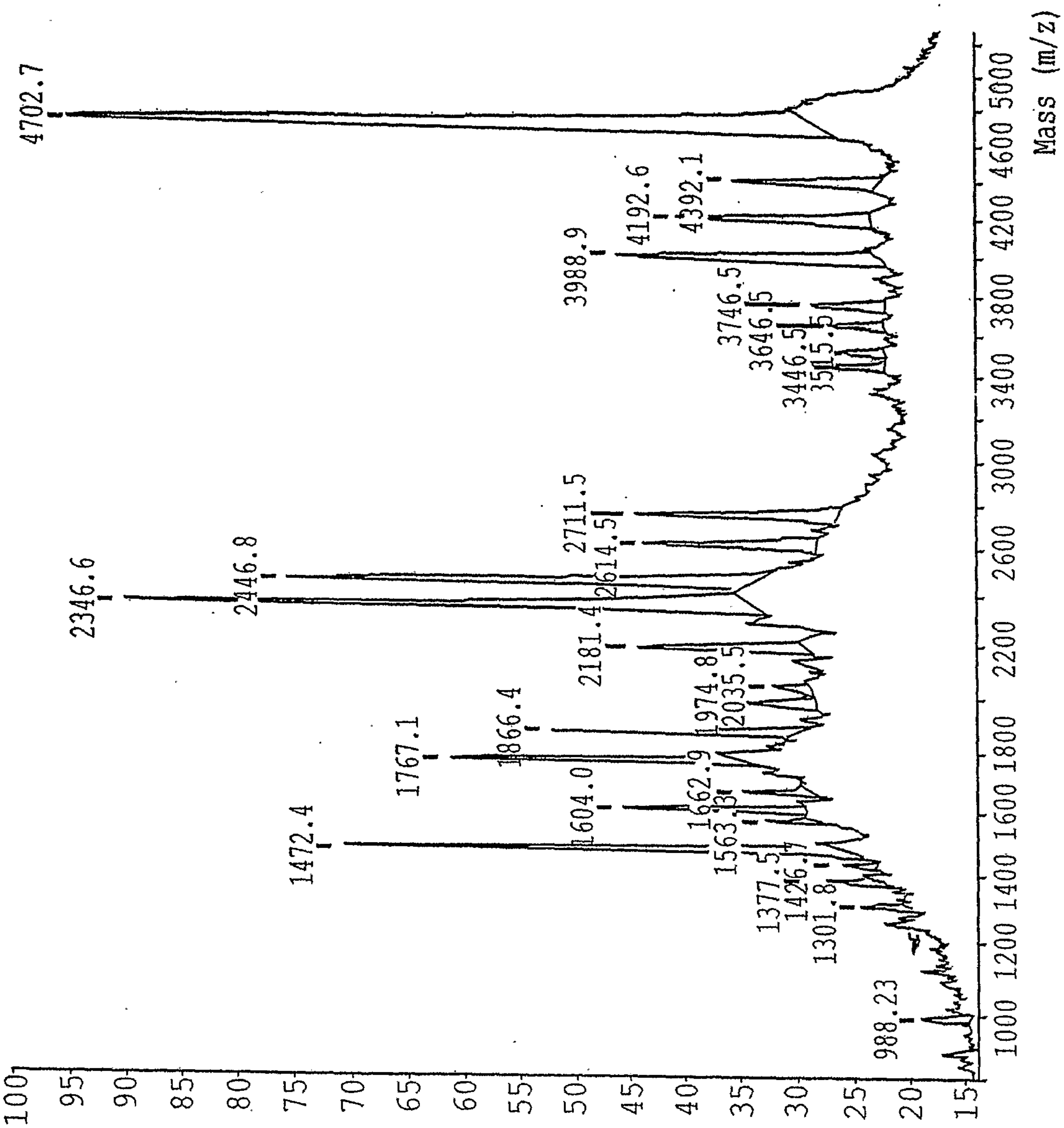
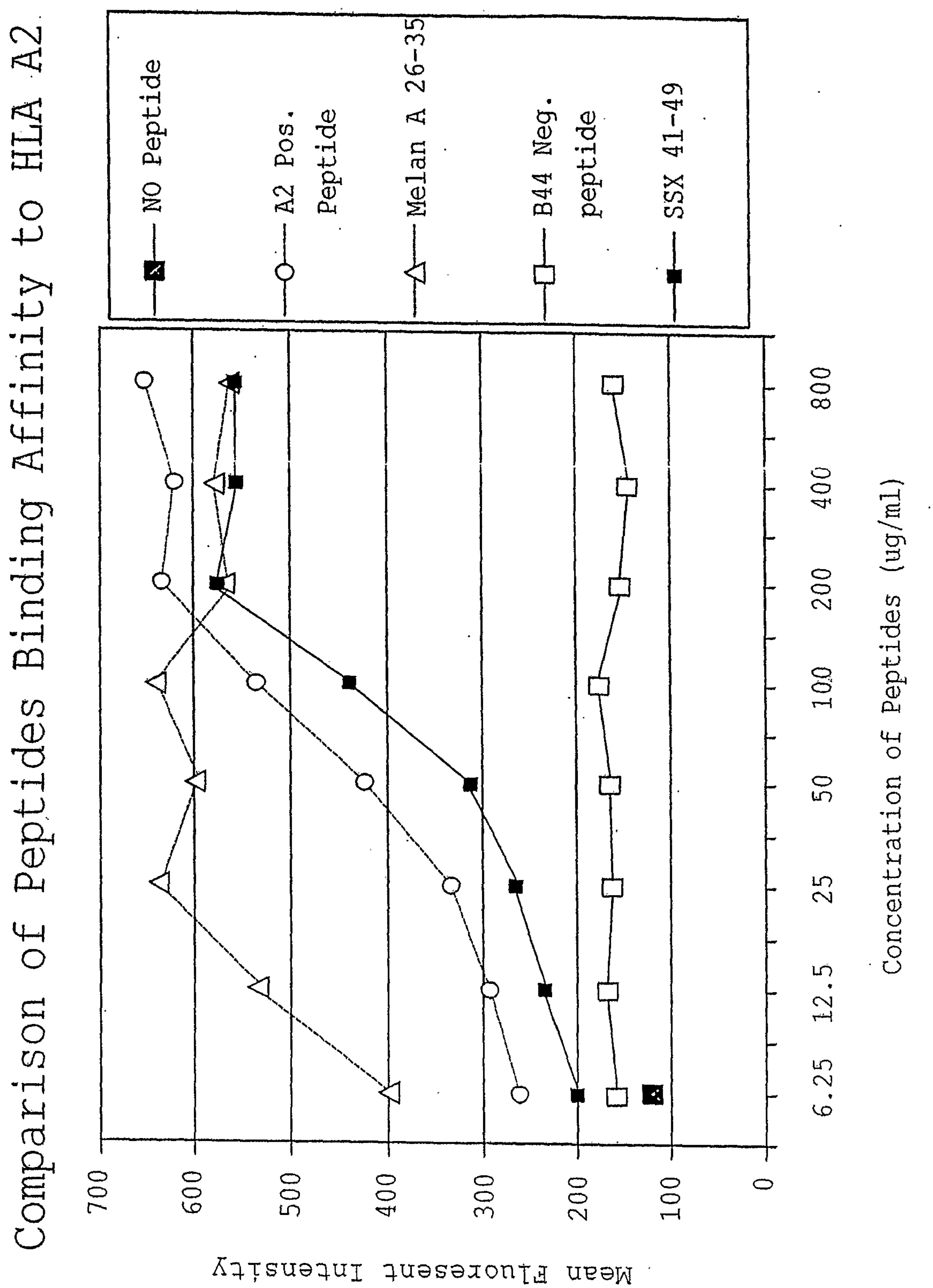

4702.7
4192.6
4392.1
3988.9
3746.5
3646.5
3446.5
2711.5
2614.5
2346.6
2446.8
2181.4
2035.5
1974.8
1866.4
1767.1
1662.9
1604.0
1563.3
1472.4
1426.7
1377.5
1301.8
988.23
Mass (m/z)
1000
1200
1400
1600
1800
2000
2200
2400
2600
2800
3000
3200
3400
3600
3800
4000
4200
4400
4600
4800
5000
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15

FIG. 4

FIG. 5


Comparison of Peptides Binding Affinity to HLA A2
NO Peptide
A2 Pos. Peptide
Melan A 26-35
B44 Neg. peptide
SSX 41-49
Mean Fluoresent Intensity
700
600
500
400
300
200
100
0
6.25
12.5
25
50
100
200
400
800
Concentration of Peptides (ug/ml)

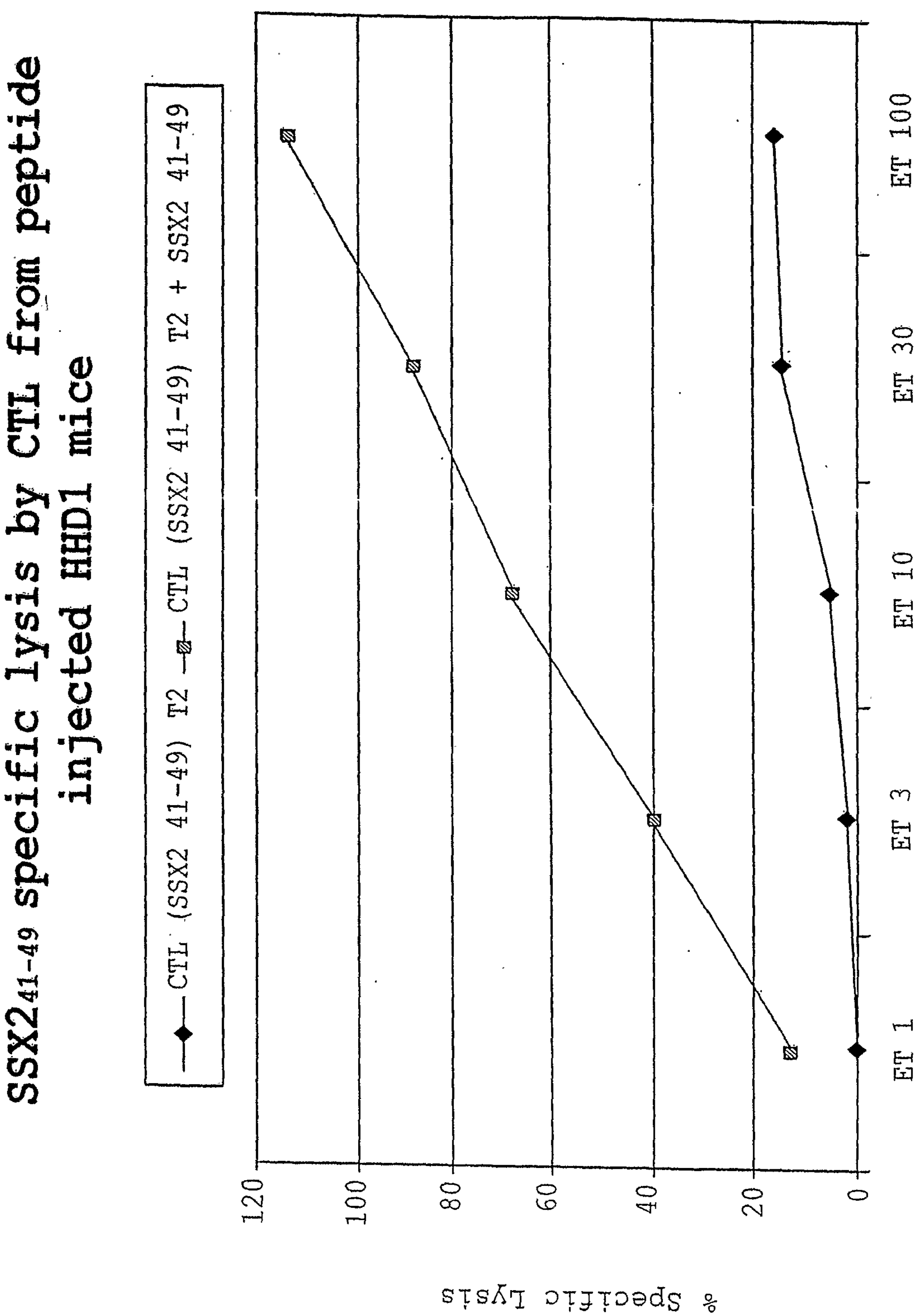
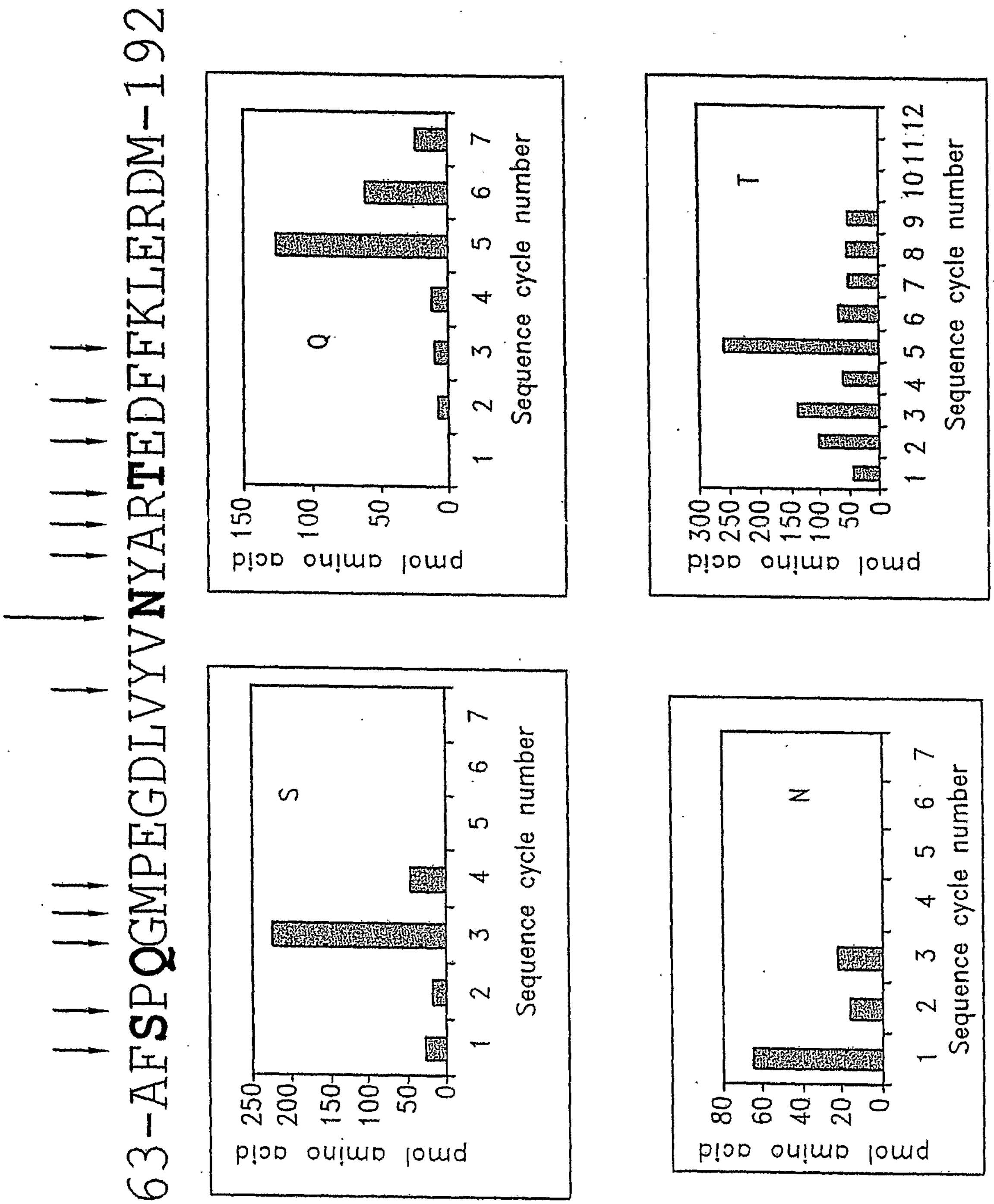

SSX2$_{41-49}$ specific lysis by CTL from peptide injected HHD1 mice
CTL (SSX2 41-49) T2
CTL (SSX2 41-49) T2 + SSX2 41-49
% Specific Lysis
120
100
80
60
40
20
0
ET 1
ET 3
ET 10
ET 30
ET 100

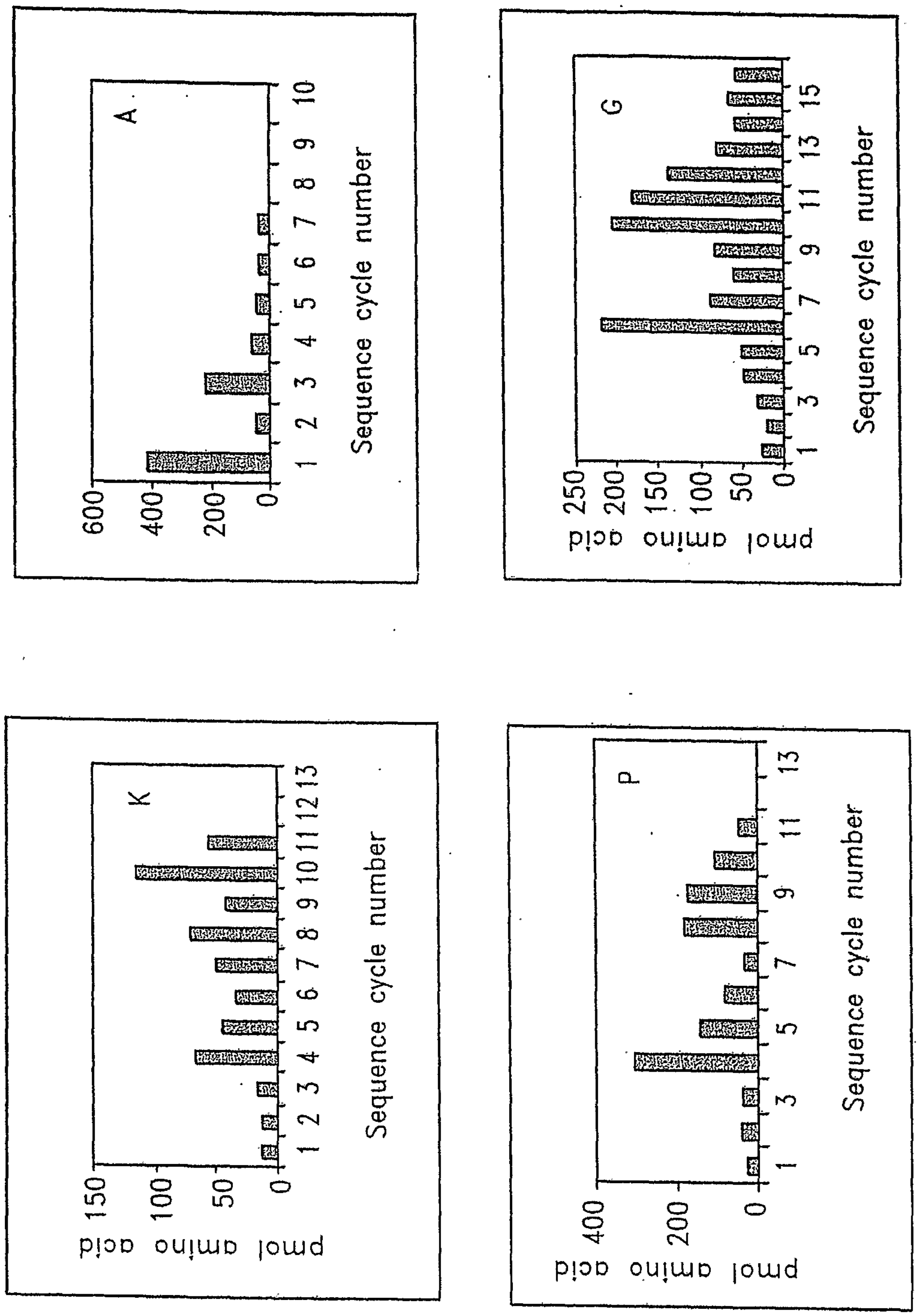
FIG. 6

FIG. 7A

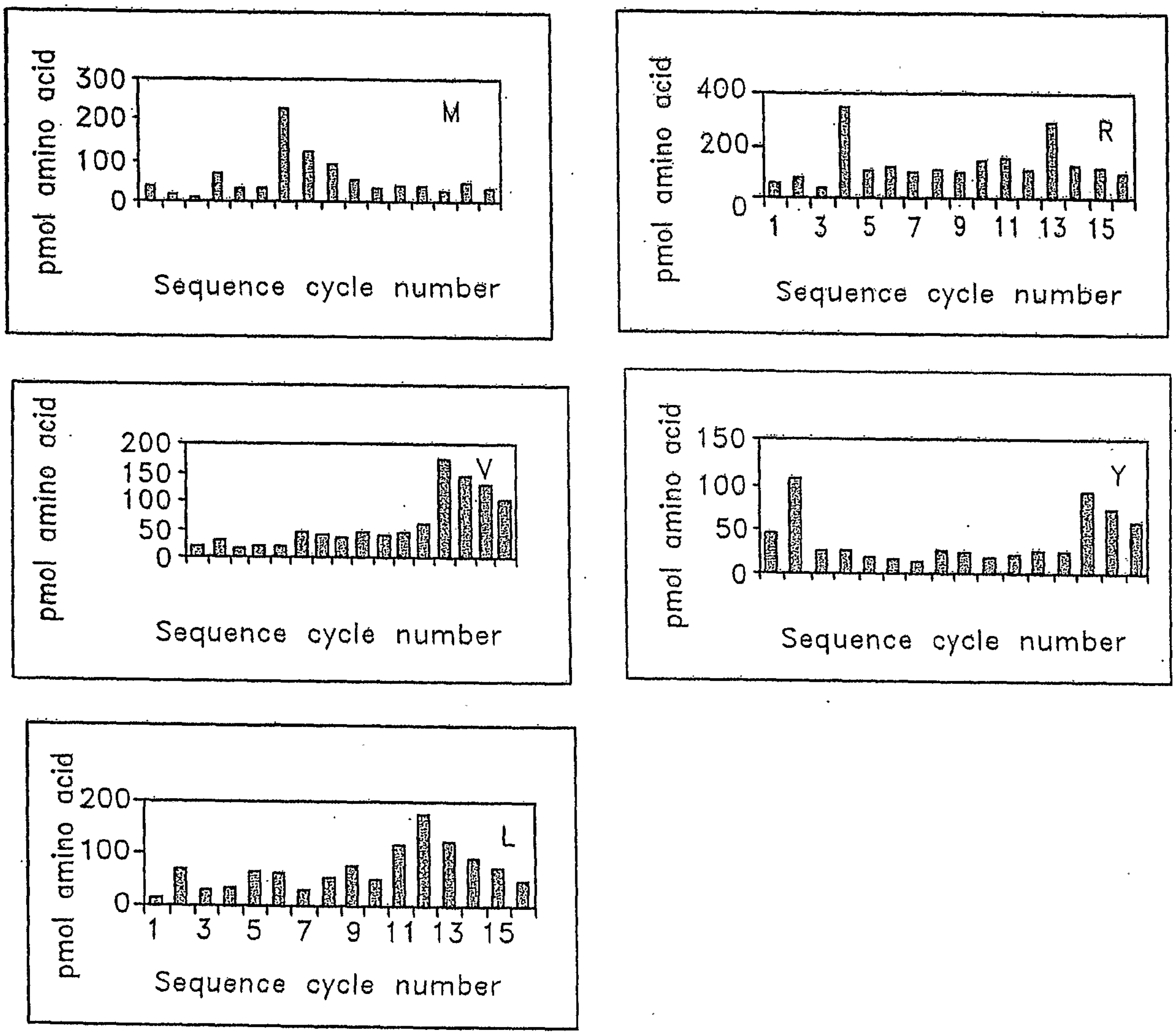


Pool sequencing of PSMA_163-192 Digested for 60 min by proteasome

FIG. 7B



Pool sequencing of PSMA_163-192 Digested for 60 min by proteasome



Pool sequencing of PSMA_163-192 Digested for 60 min by proteasome

FIG. 7C

FIG. 8

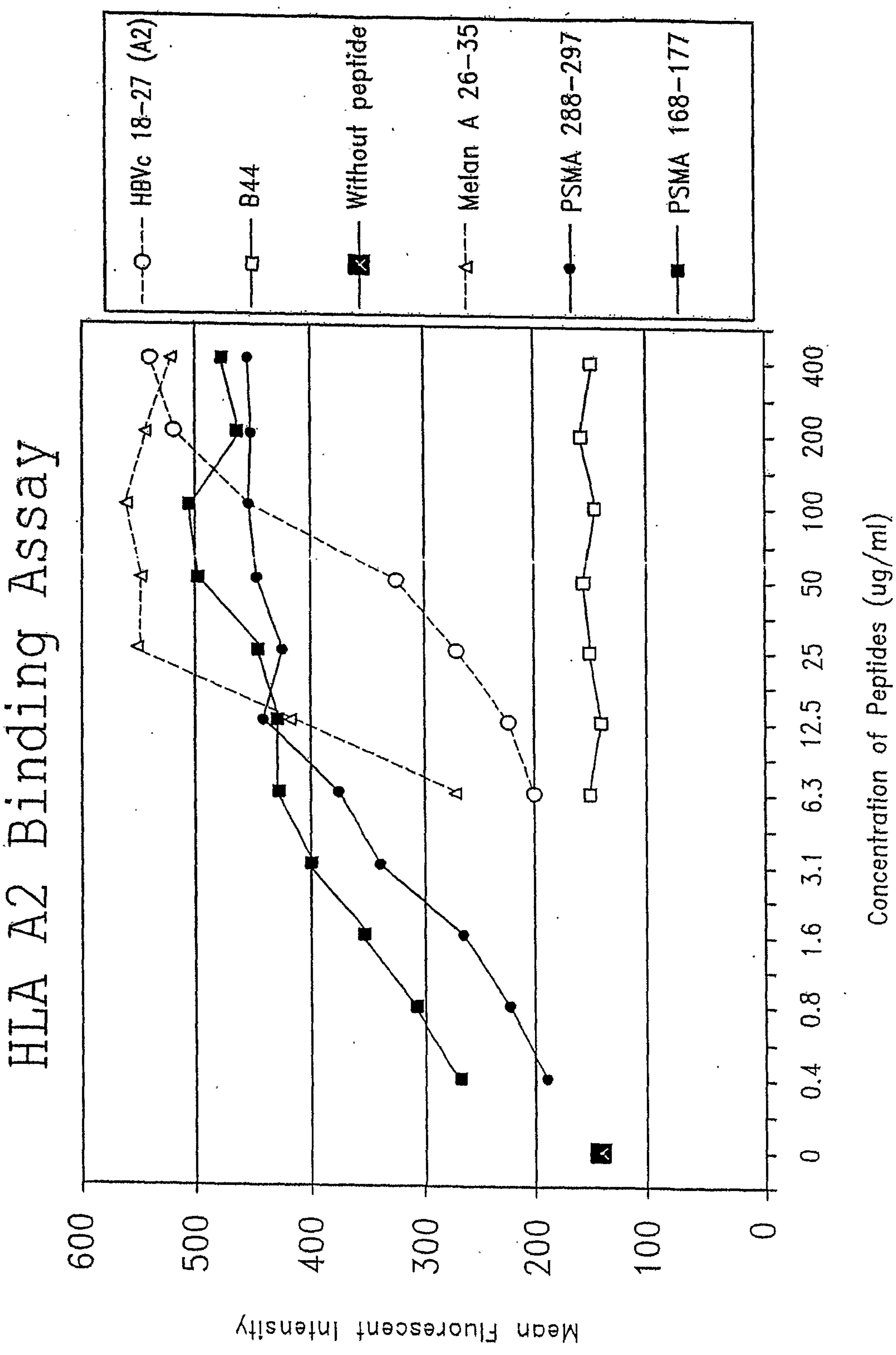
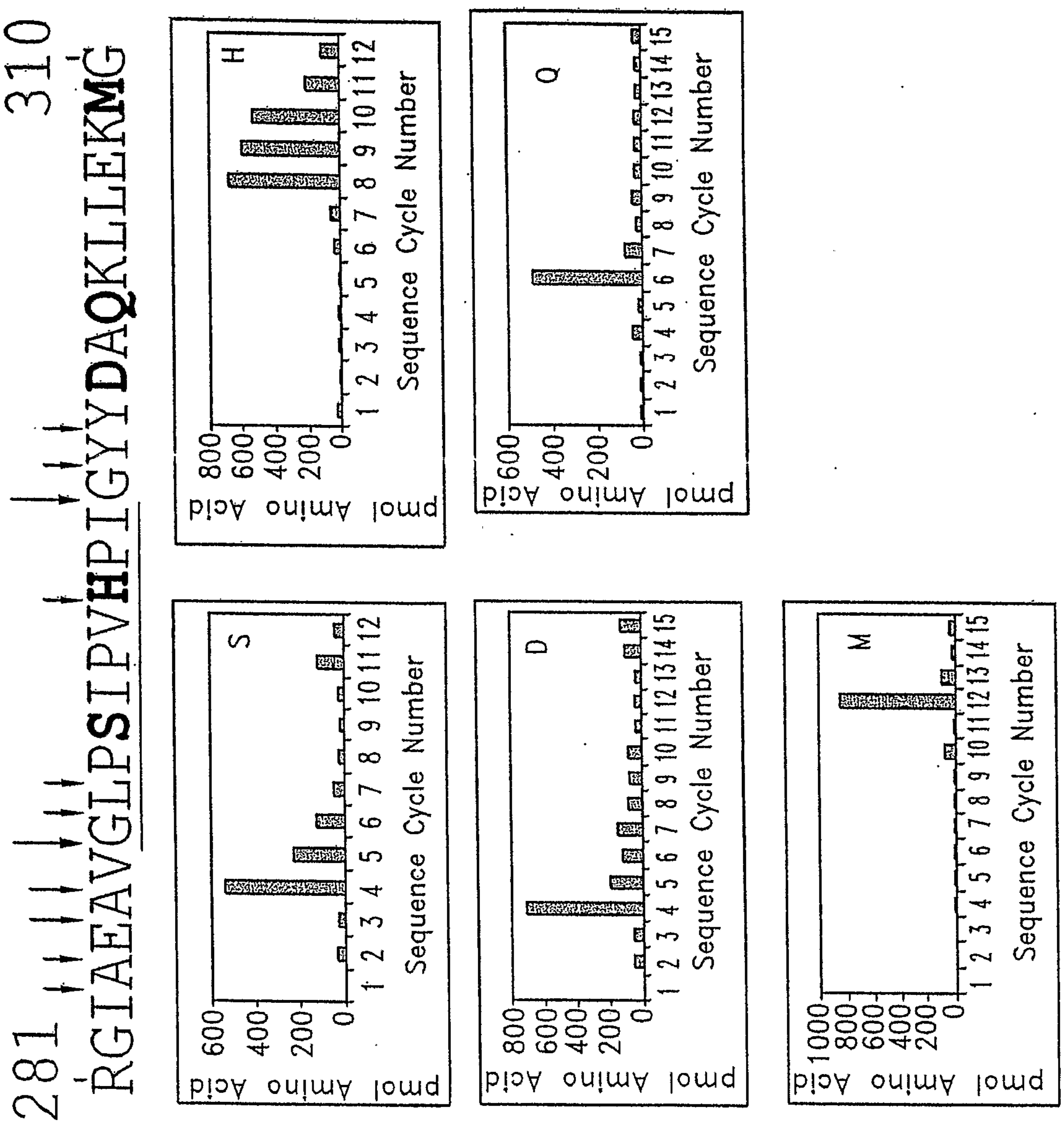

HLA A2 Binding Assay
HBVc 18-27 (A2)
B44
Without peptide
Melan A 26-35
PSMA 288-297
PSMA 168-177
Mean Fluorescent Intensity
0
100
200
300
400
500
600
Concentration of Peptides (ug/ml)
0
0.4
0.8
1.6
3.1
6.3
12.5
25
50
100
200
400

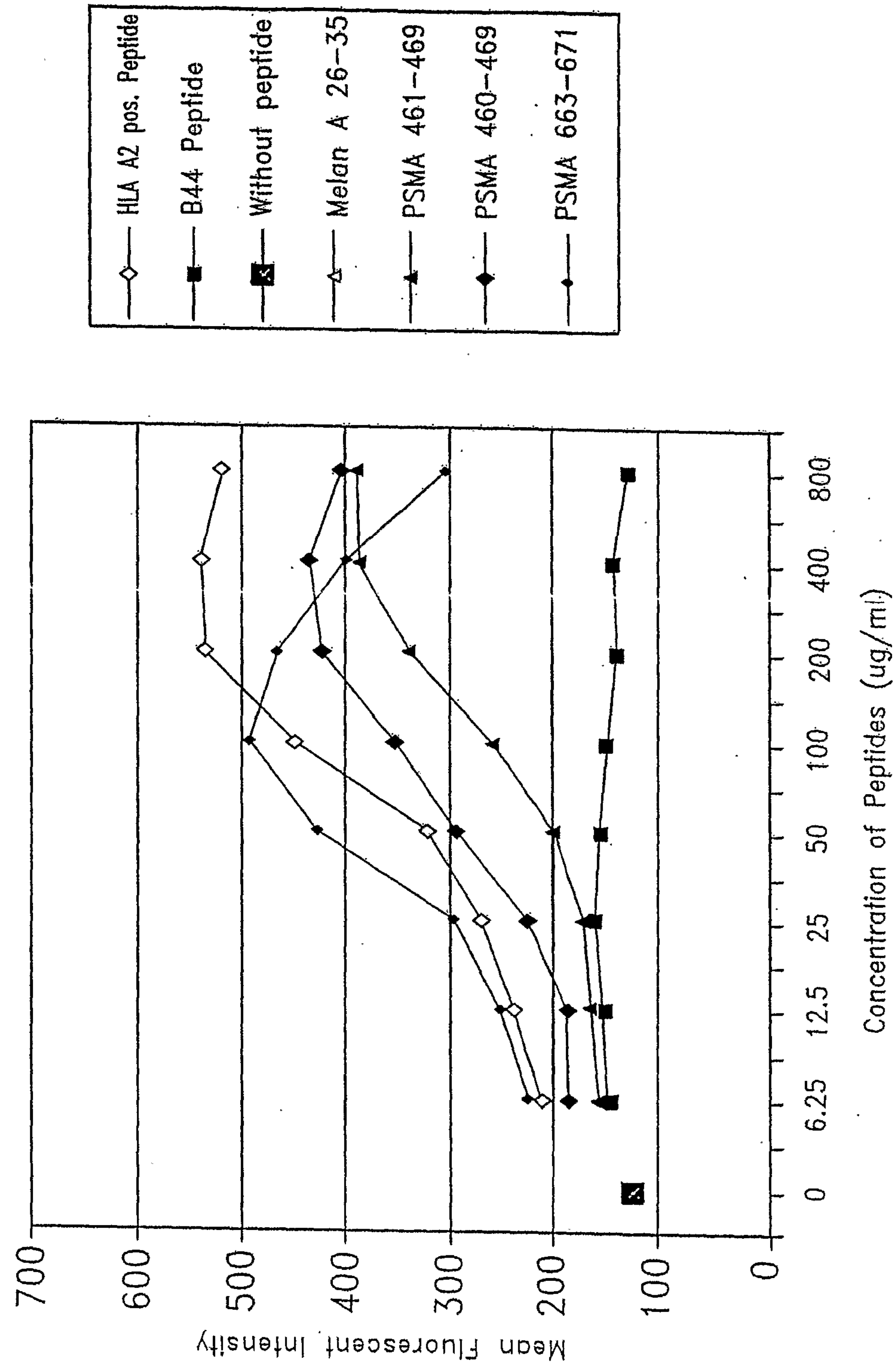
FIG. 9



Pool sequencing of PSMA_281_310 Digested for 60 min by Proteasome

FIG. 10

Comparison of Peptides Binding Affinity to HLA A2 by Binding Assay



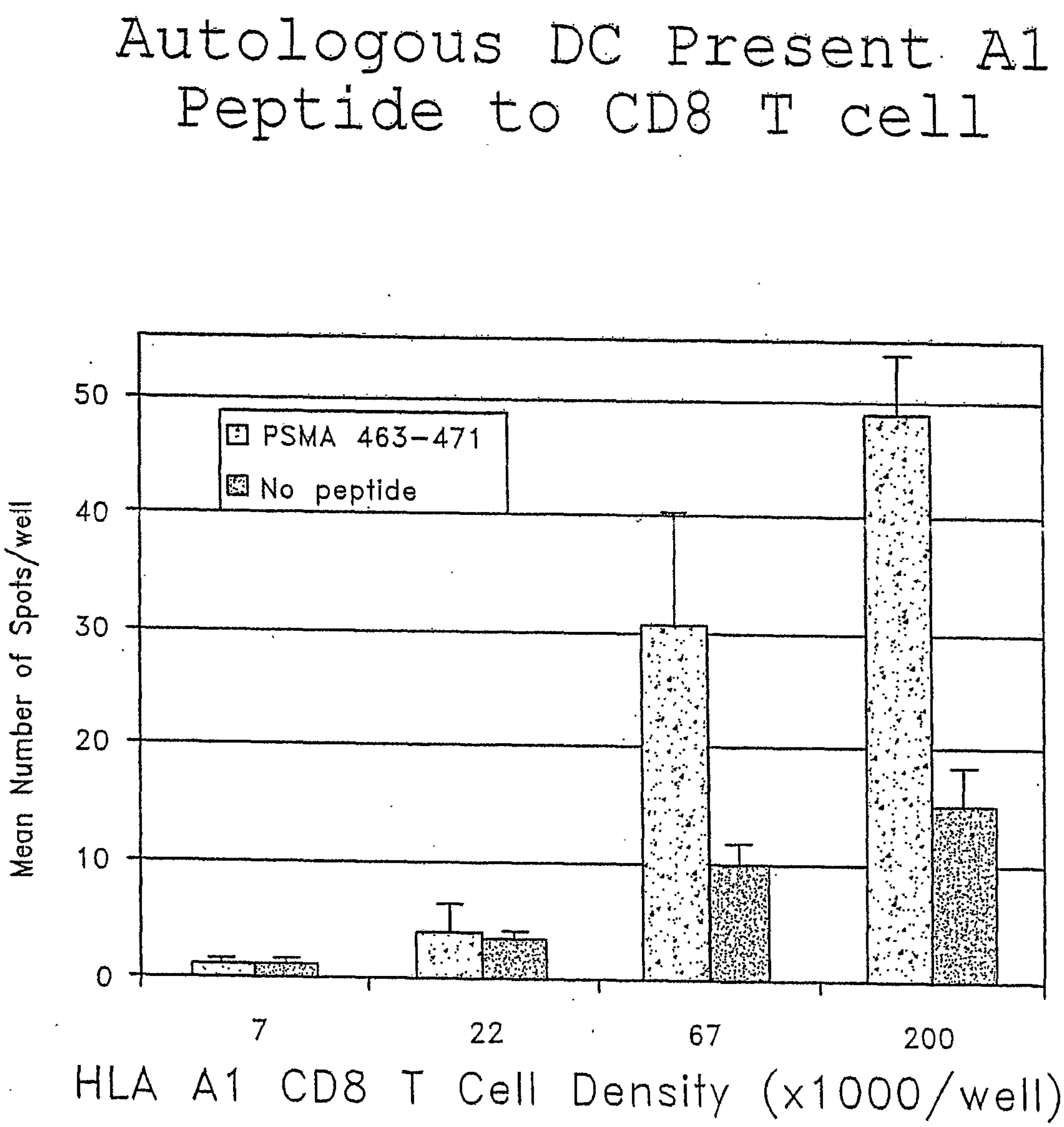

Autologous DC Present A1
Peptide to CD8 T cell
PSMA 463-471
No peptide
Mean Number of Spots/well
0
10
20
30
40
50
7
22
67
200
HLA A1 CD8 T Cell Density (x1000/well)

FIG. 11

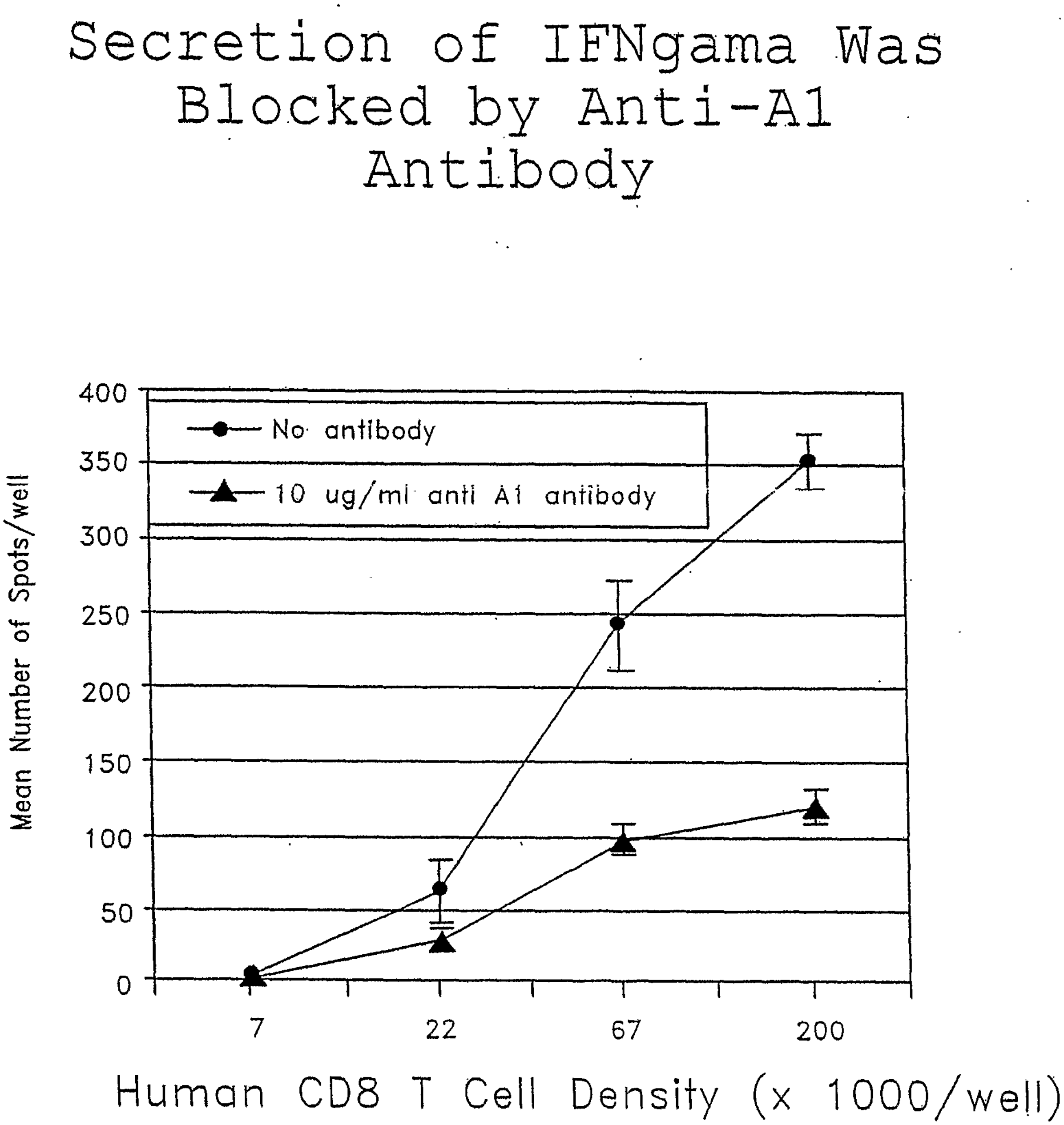

Secretion of IFNgama Was Blocked by Anti-A1 Antibody
No antibody
10 ug/ml anti A1 antibody
Mean Number of Spots/well
400
350
300
250
200
150
100
50
0
7
22
67
200
Human CD8 T Cell Density (x 1000/well)

FIG. 12

FIG. 13

Comparison of Peptides Binding Affinity to HLA A2 by Binding Assay

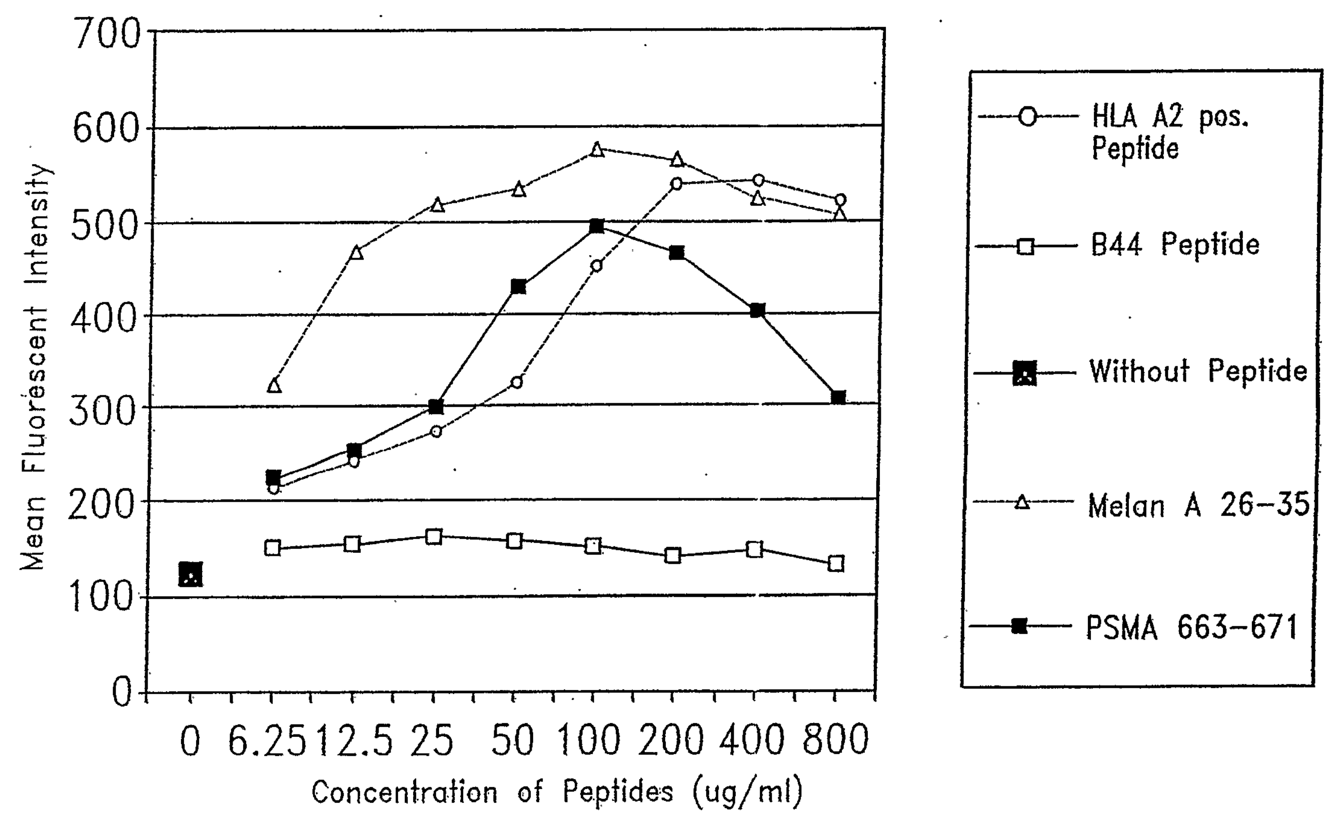
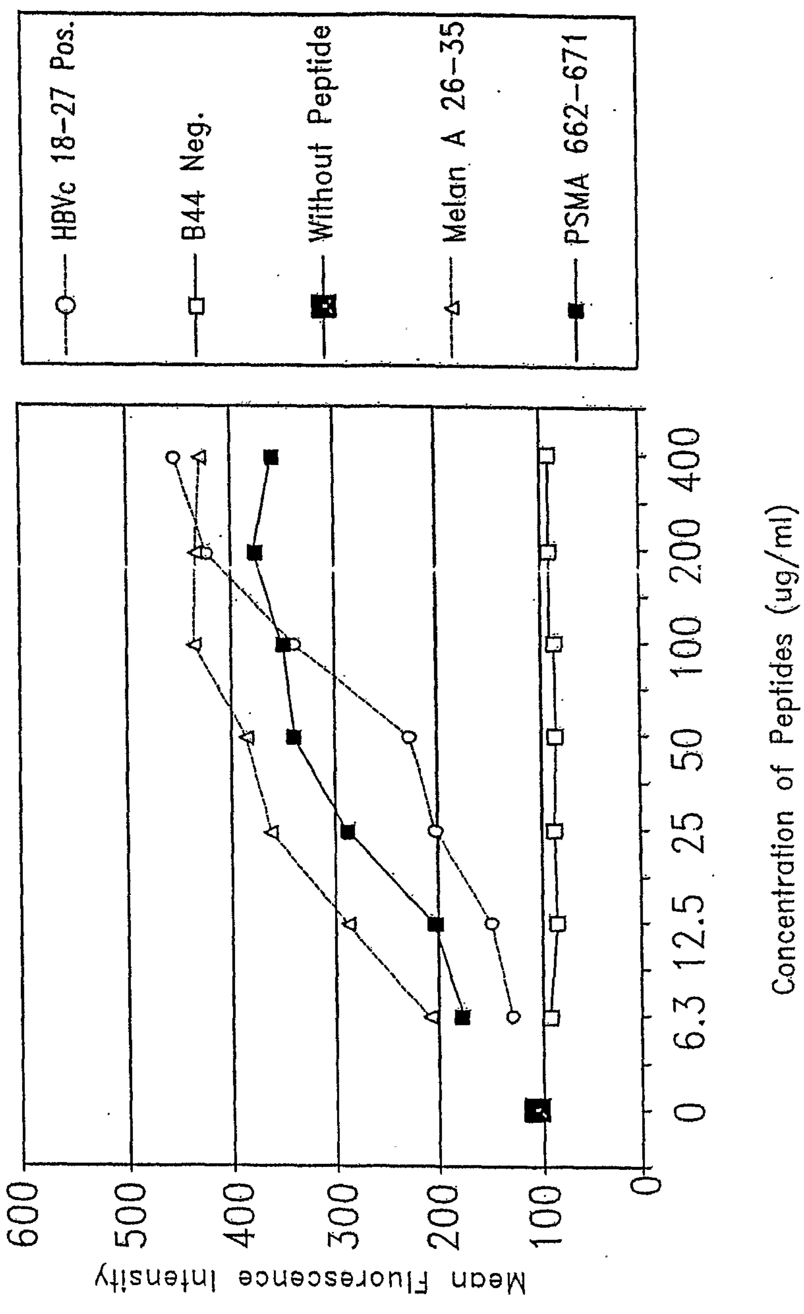
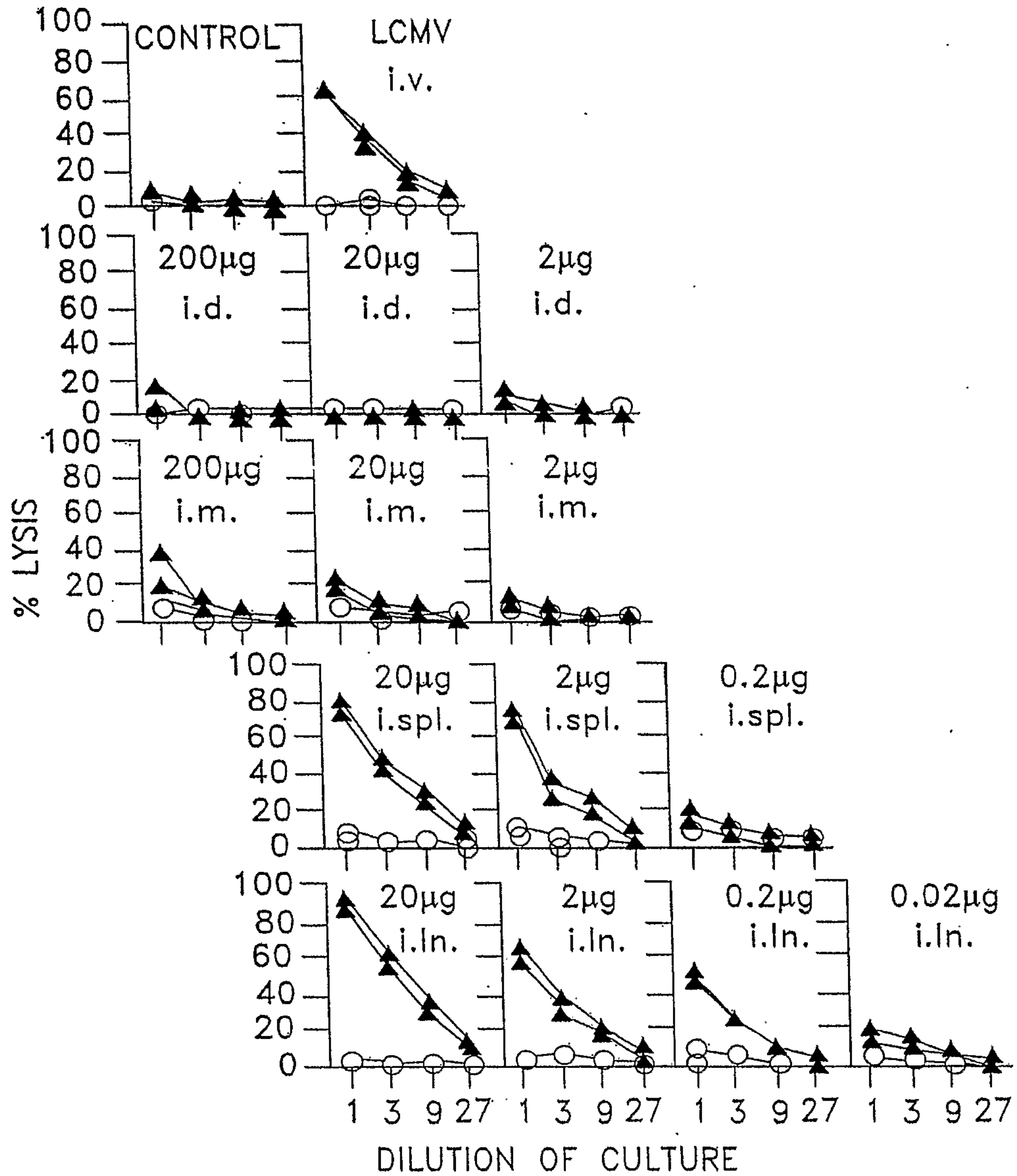


FIG. 14

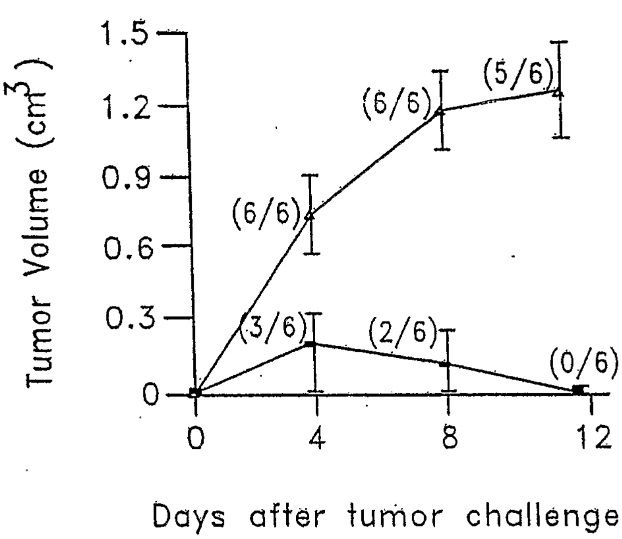
Comparison of Peptides Binding Affinity to HLA A2 by Binding Assay





Graphs show lysis of unpulsed EL4 cells (open circles) and EL4 cells pulsed with gp33 peptide (solid triangles). Symbols represent individual mice and one of three similar experiments is shown.

FIG. 15



Mean tumor volumes ± 1SD are shown for mice immunized with pEFGPL33A DNA (solid circles) or control pEGFP-N3 DNA (open triangles). Numbers in brackets indicate number of mice with tumors/total number of mice in group. One of two similar experiments is shown.

FIG. 16

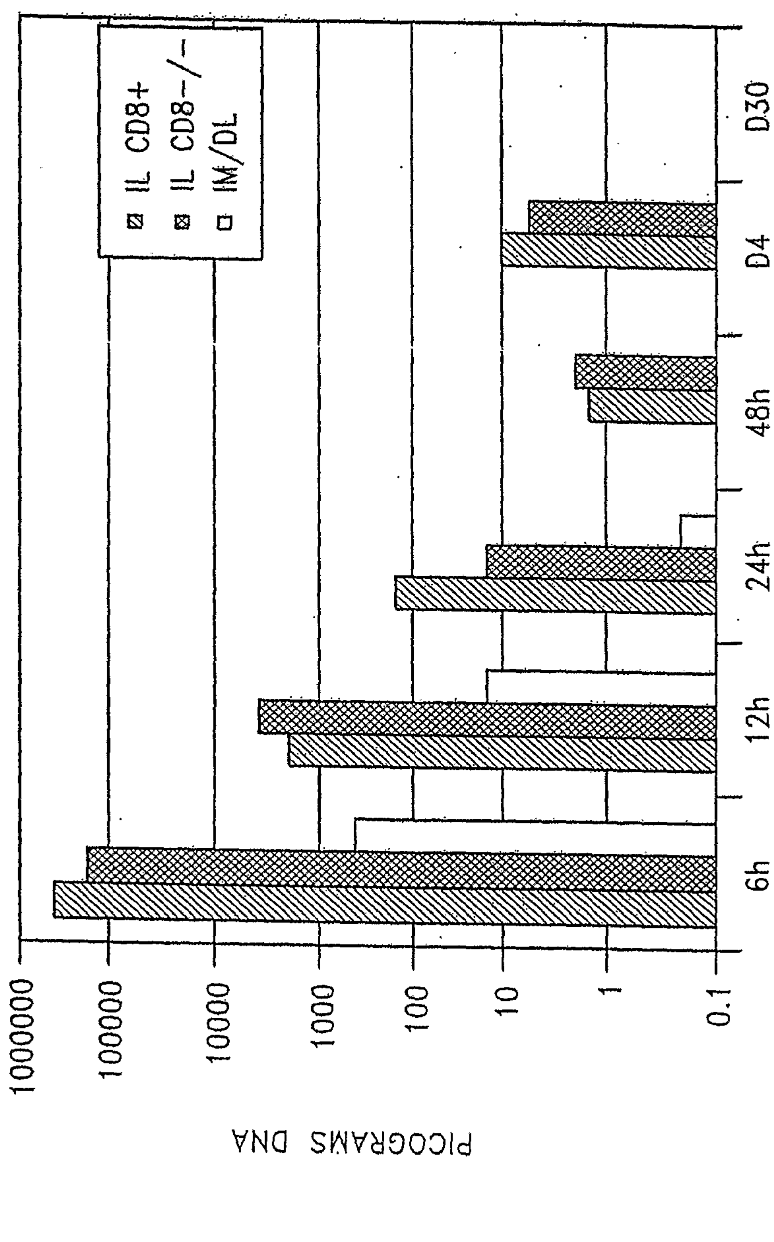

IL CD8+
IL CD8-/-
IM/DL
PICOGRAMS DNA
1000000
100000
10000
1000
100
10
1
0.1
6h
12h
24h
48h
D4
D30

FIG. 17

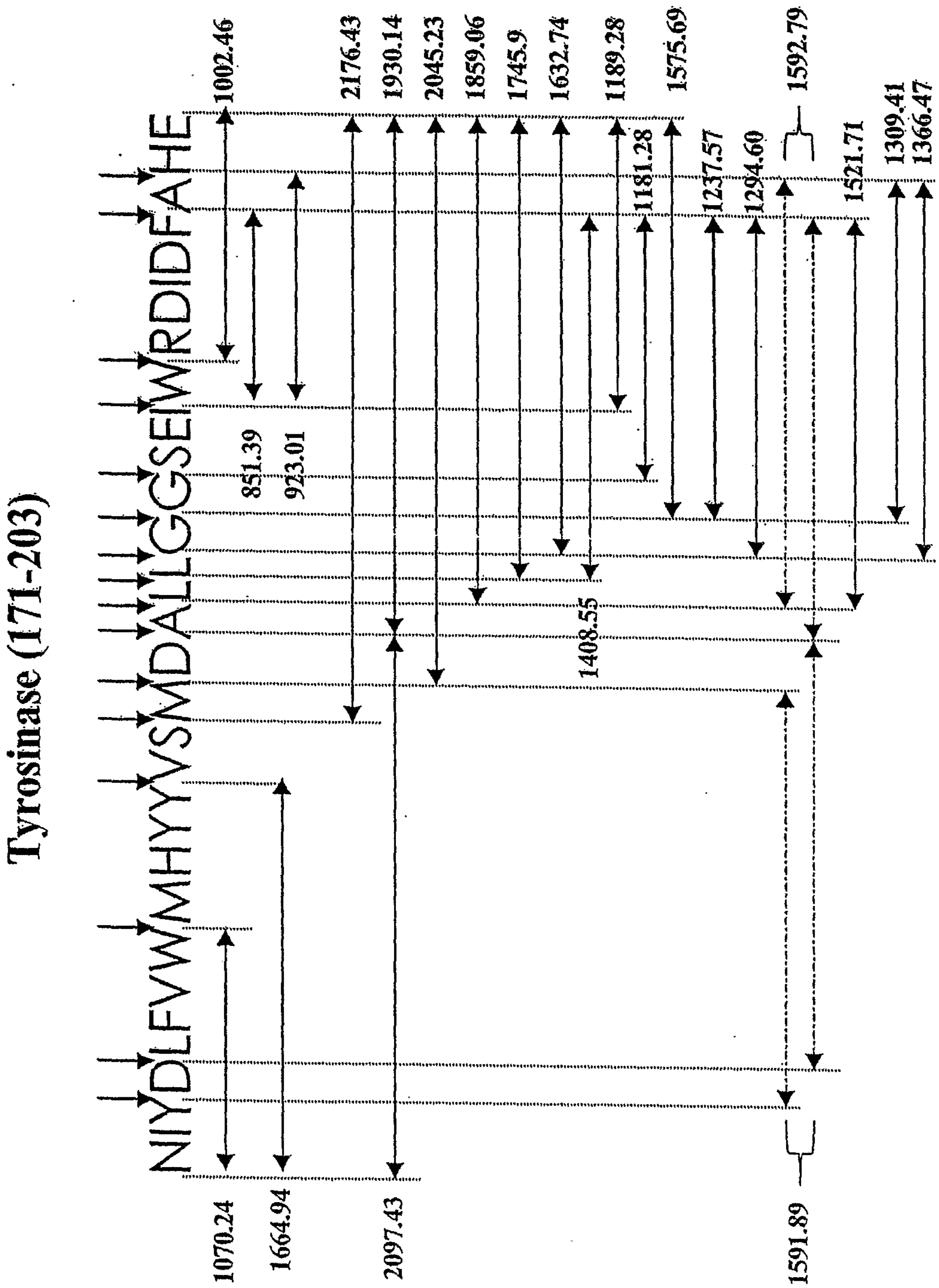

Tyrosinase (171-203)
NIYDLFVWMHYYVSMDALLGGSEIWRDIDFAHE
1002.46
851.39
923.01
2176.43
1930.14
2045.23
1859.06
1745.9
1632.74
1408.55
1189.28
1181.28
1575.69
1237.57
1294.60
1592.79
1521.71
1309.41
1366.47
1070.24
1664.94
2097.43
1591.89

Figure 18

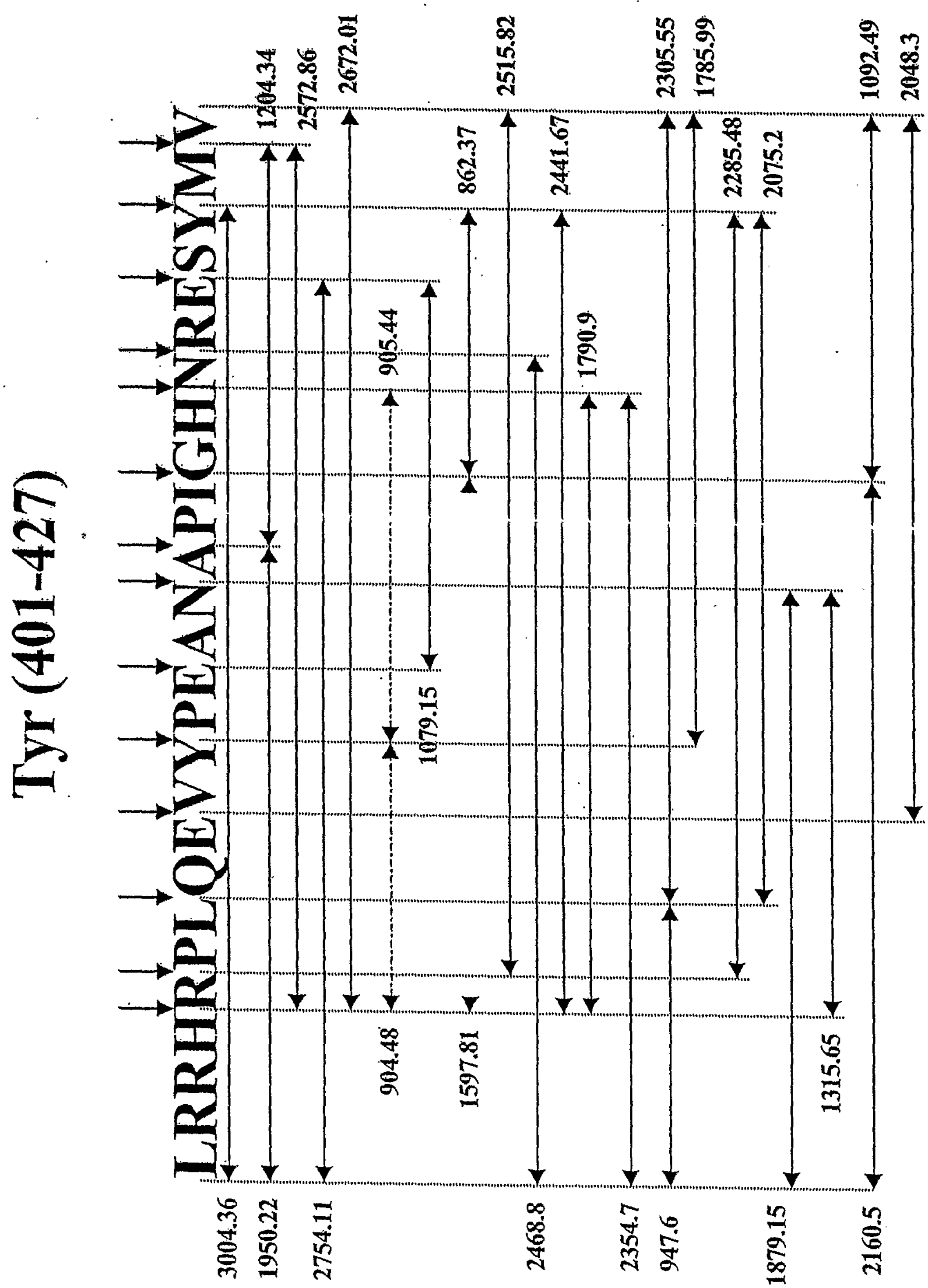

Tyr (401-427)
3004.36
1950.22
2754.11
2468.8
2354.7
947.6
1879.15
2160.5
904.48
1597.81
1315.65
905.44
1079.15
862.37
1790.9
2441.67
2285.48
2075.2
1204.34
2572.86
2672.01
2515.82
2305.55
1785.99
1092.49
2048.3

Figure 19

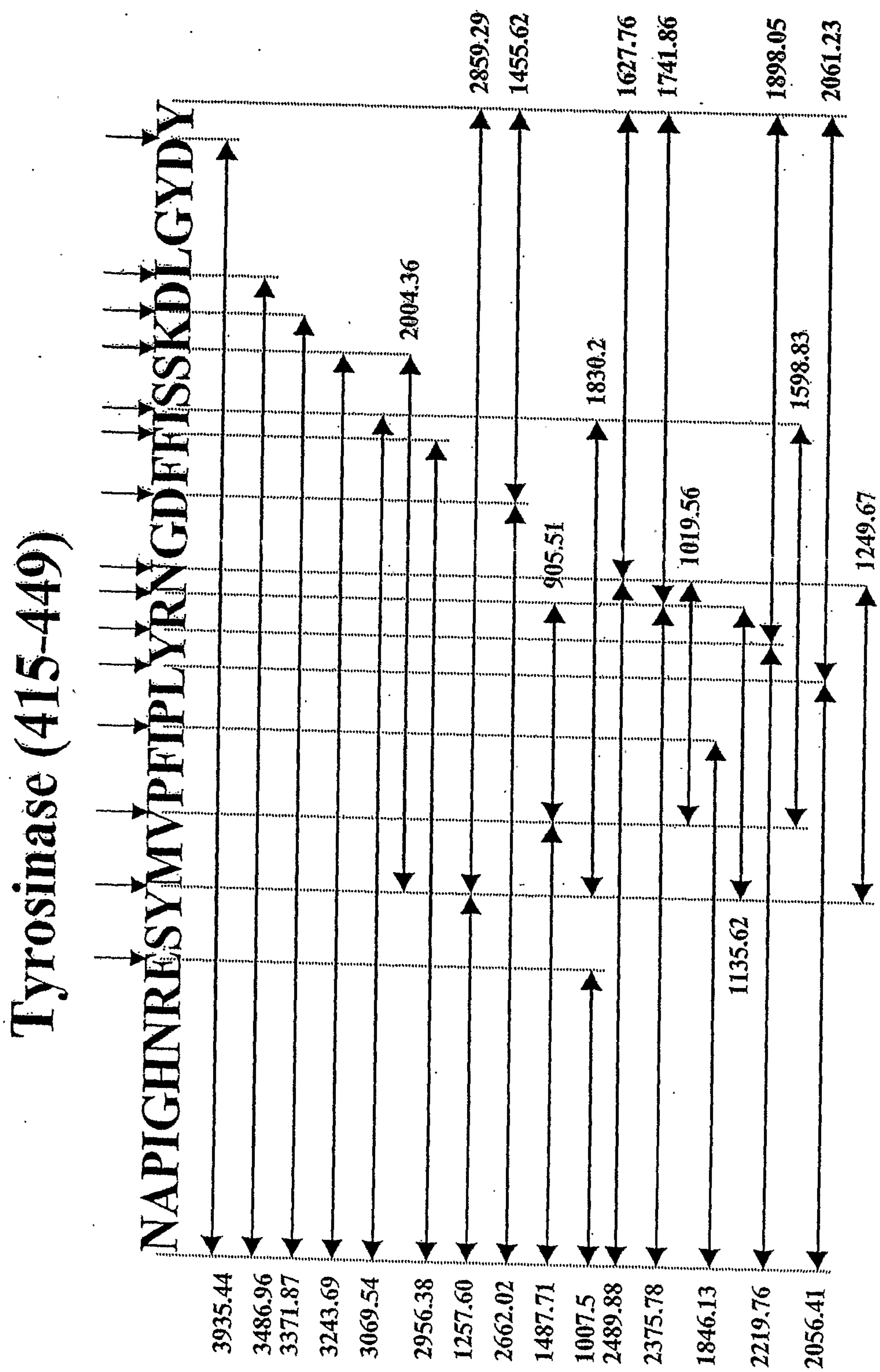

Tyrosinase (415-449)
NAPIGHNRESYMVPFIPLYRNGDFFISSKDLGYDY
3935.44
3486.96
3371.87
3243.69
3069.54
2956.38
1257.60
2662.02
1487.71
1007.5
2489.88
2375.78
1846.13
2219.76
2056.41
2004.36
2859.29
1455.62
905.51
1830.2
1627.76
1741.86
1019.56
1135.62
1898.05
1598.83
2061.23
1249.67

Figure 20

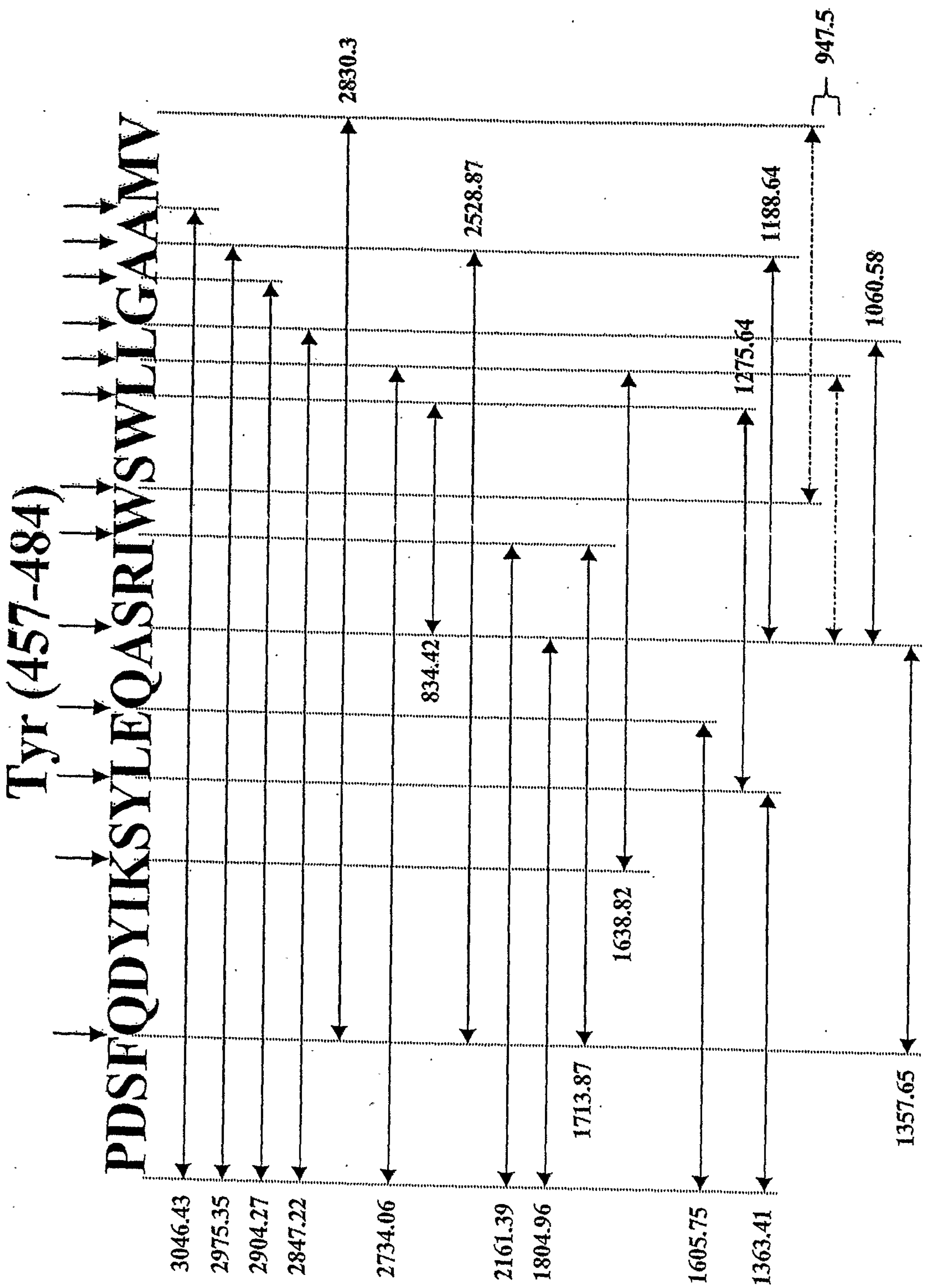

Tyr (457-484)
PDSFQDYIKSYLEQASRIWSWLLGAAMV
2830.3
947.5
2528.87
1188.64
1060.58
1275.64
834.42
1638.82
1713.87
1357.65
3046.43
2975.35
2904.27
2847.22
2734.06
2161.39
1804.96
1605.75
1363.41

Figure 21

CEA 92-118

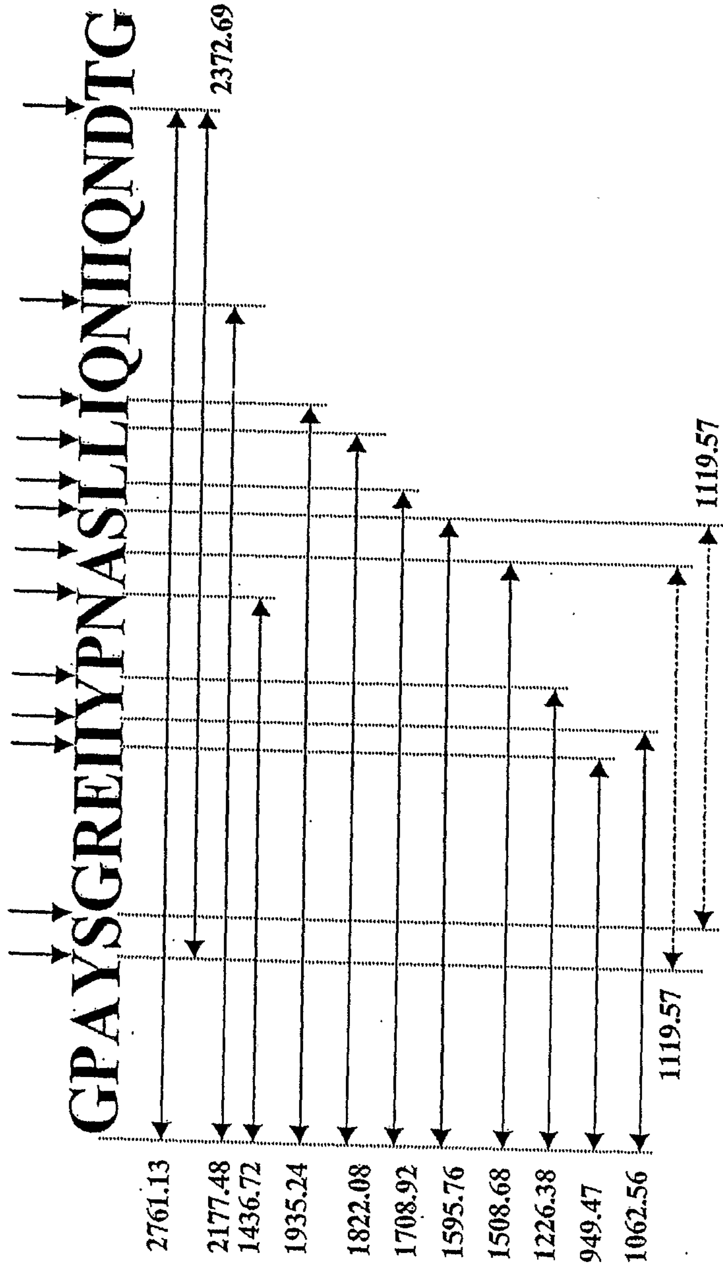


Figure 22

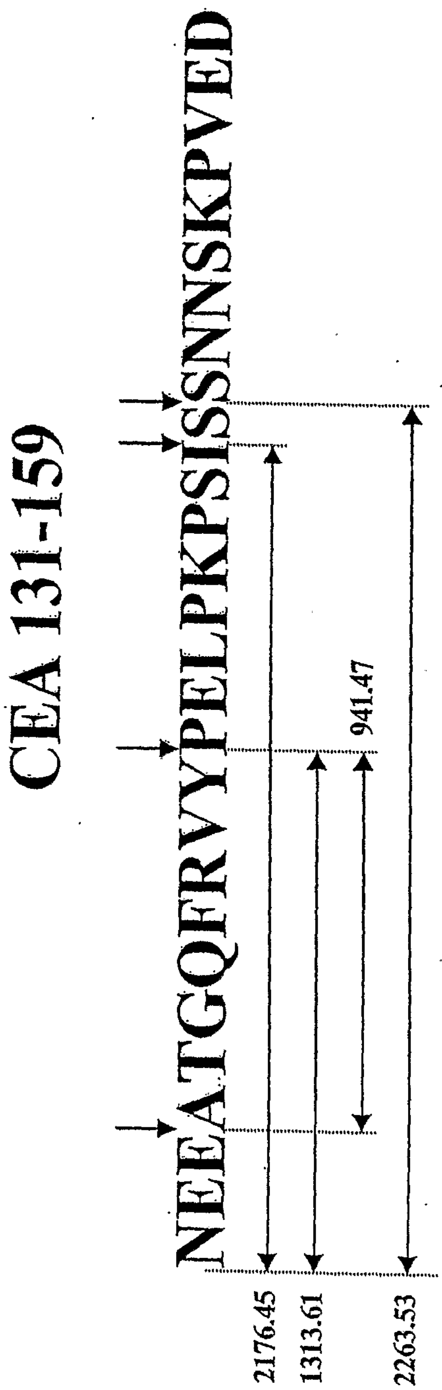

CEA 131-159
NEEATGQFRVVYPELPKPSISSNNSKPVED
941.47
2176.45
1313.61
2263.53

Figure 23

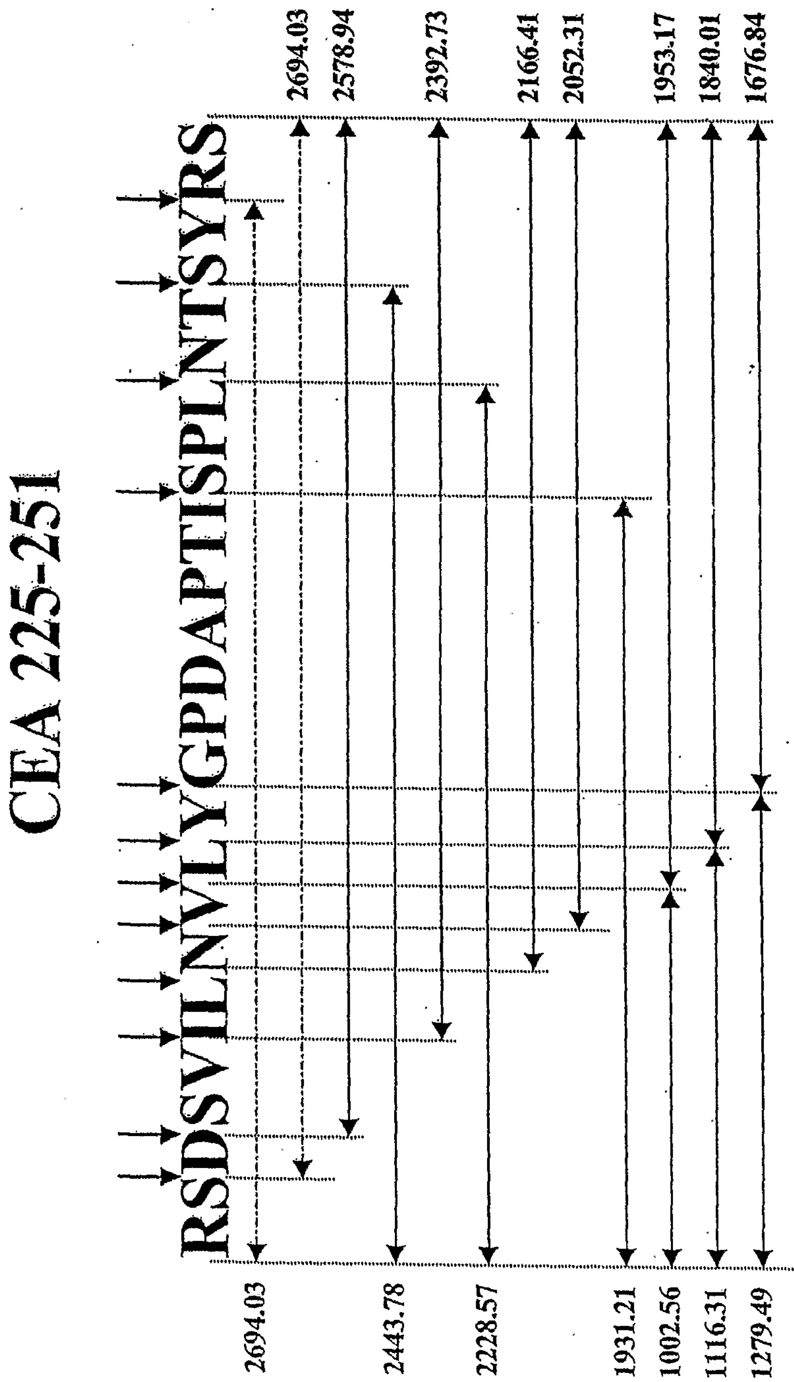

CEA 225-251
RSDSVIILNVLYGPDAPTISPLNTSYRS
2694.03
2578.94
2392.73
2166.41
2052.31
1953.17
1840.01
1676.84
2694.03
2443.78
2228.57
1931.21
1002.56
1116.31
1279.49

Figure 24

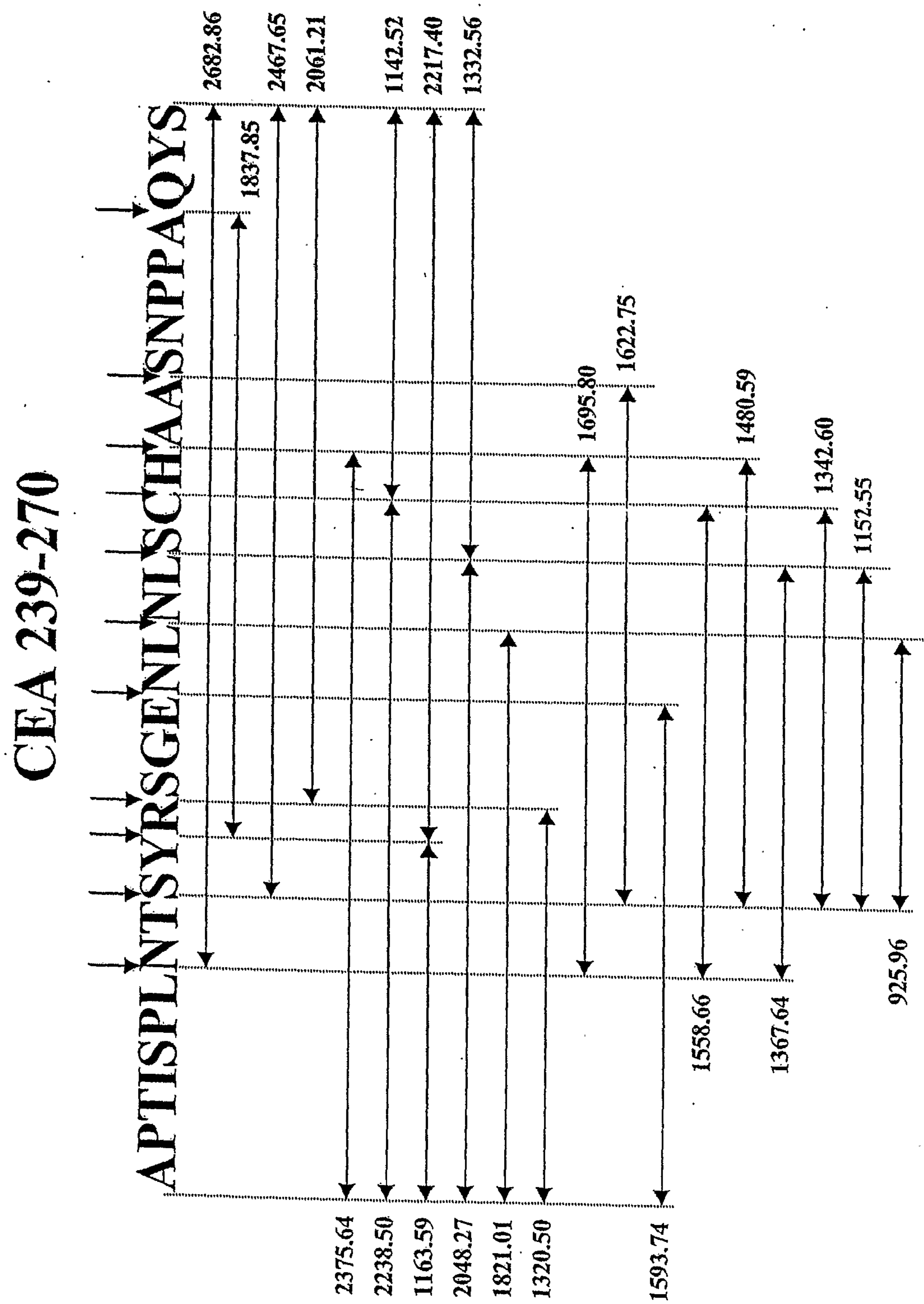

CEA 239-270
APTISPLNTSYRSGENLNLSCHAASNPPAQYS
2682.86
1837.85
2467.65
2061.21
1142.52
2217.40
1332.56
1695.80
1622.75
1480.59
1342.60
1152.55
925.96
1558.66
1367.64
2375.64
2238.50
1163.59
2048.27
1821.01
1320.50
1593.74

Figure 25

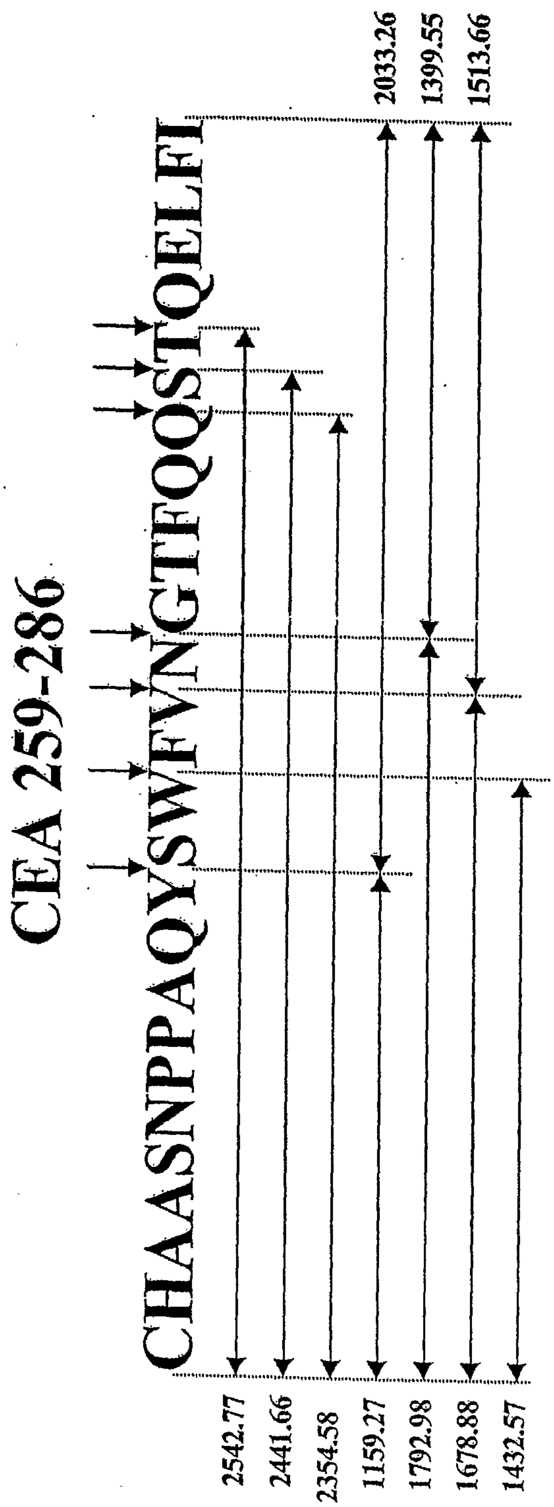

CEA 259-286
CHAASNPPAQYSWFVNGTFQQSTQELFI
2033.26
1399.55
1513.66
2542.77
2441.66
2354.58
1159.27
1792.98
1678.88
1432.57

Figure 26

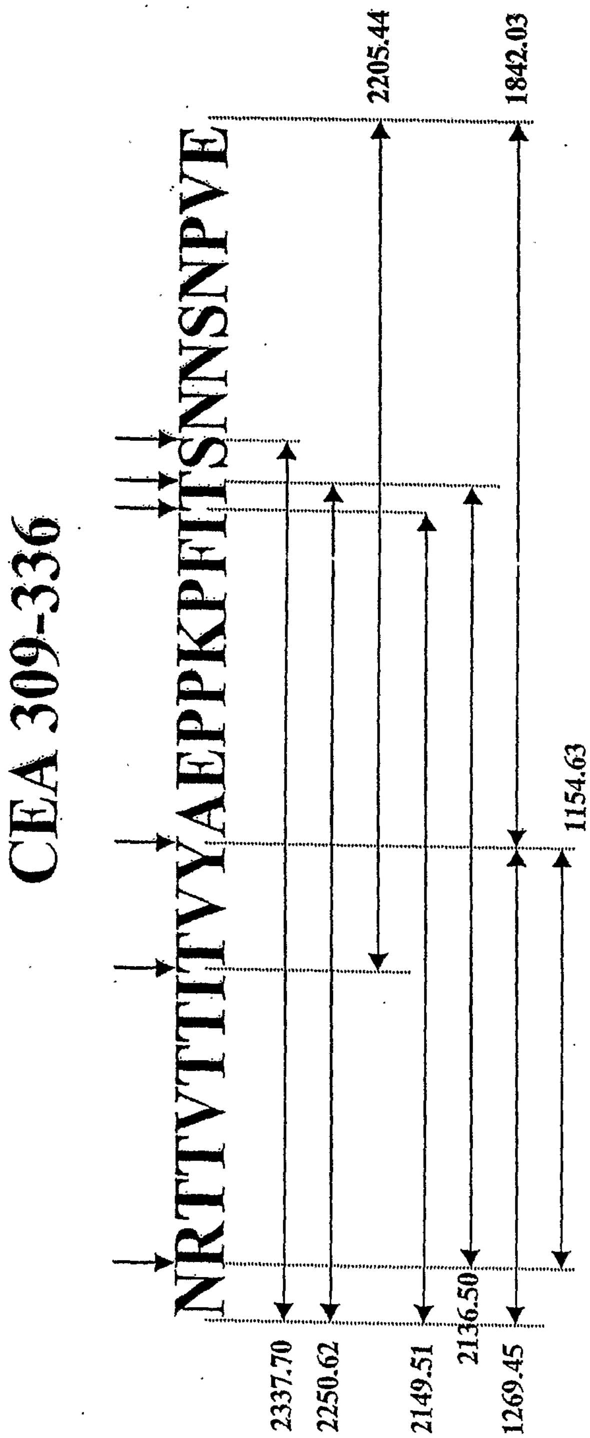

CEA 309-336
NRTTTVTTITVYAEPPKPFITSNNSNPVE
2205.44
1842.03
1154.63
2337.70
2250.62
2149.51
2136.50
1269.45

Figure 27

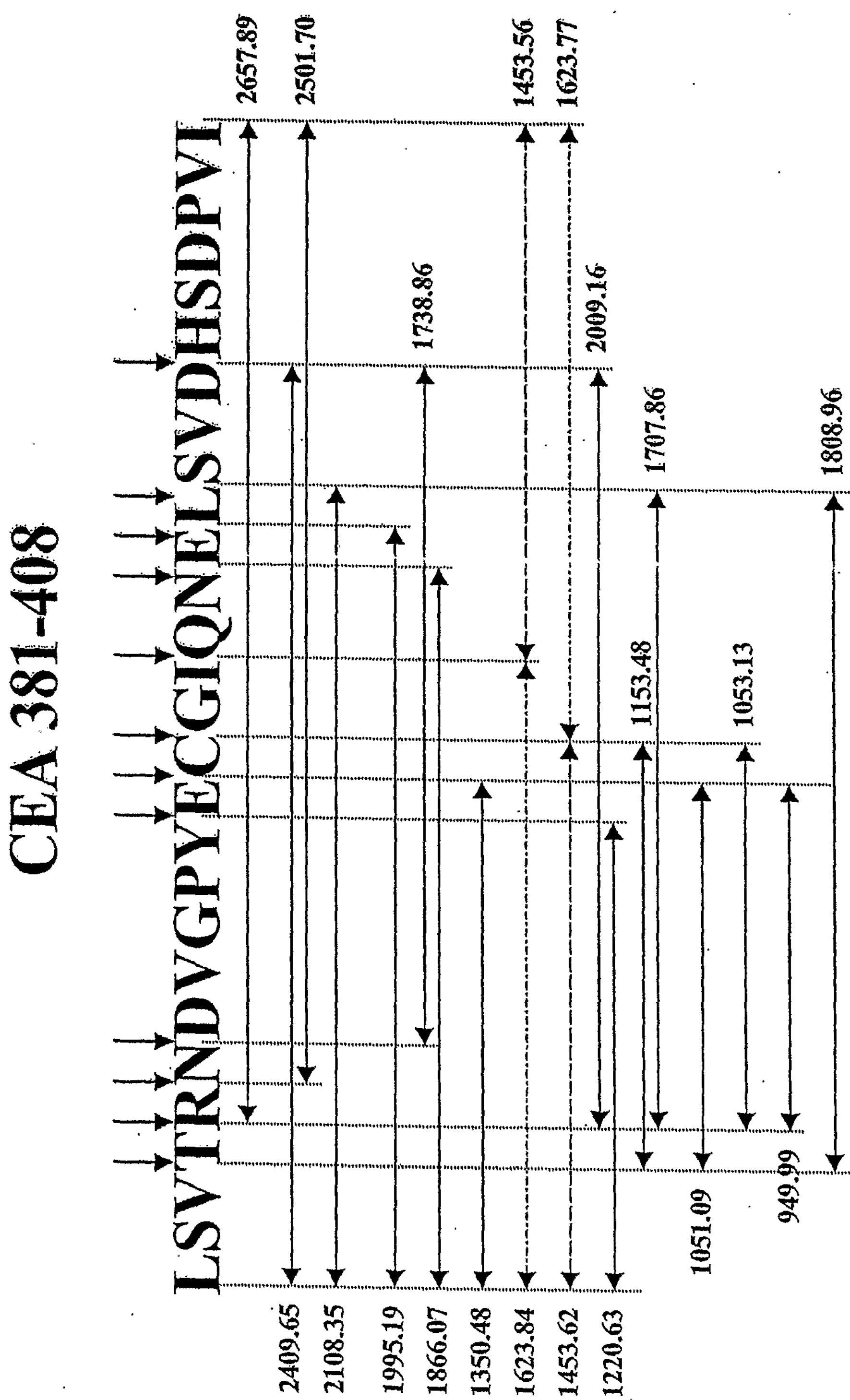

CEA 381-408
LSVTRNDVGPYECGIQNELSVDHSDPVI
2657.89
2501.70
1453.56
1623.77
1738.86
2009.16
1707.86
1808.96
1153.48
1053.13
2409.65
2108.35
1995.19
1866.07
1350.48
1623.84
1453.62
1220.63
1051.09
949.99

Figure 28

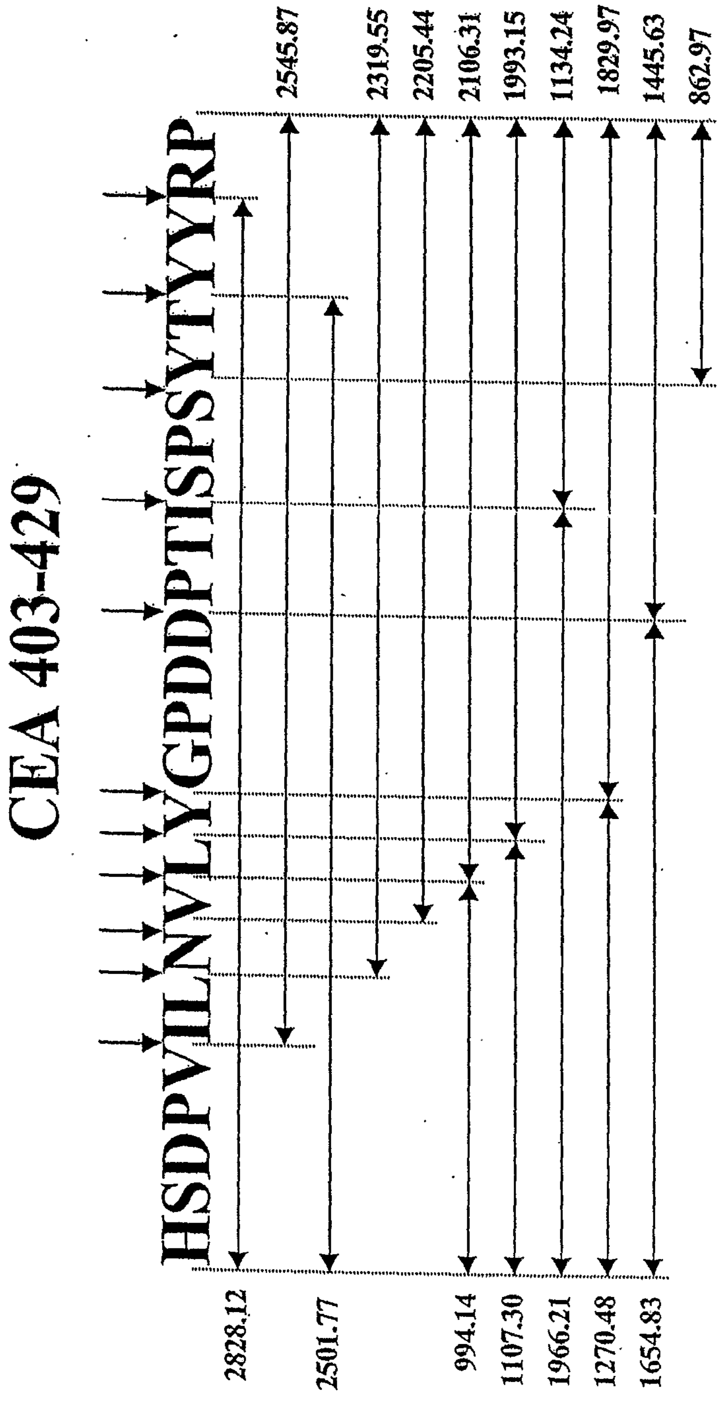

CEA 403-429
HSDPVIILNVLYGPDDPTISPSYTYYRP
2545.87
2319.55
2205.44
2106.31
1993.15
1134.24
1829.97
1445.63
862.97
2828.12
2501.77
994.14
1107.30
1966.21
1270.48
1654.83

Figure 29

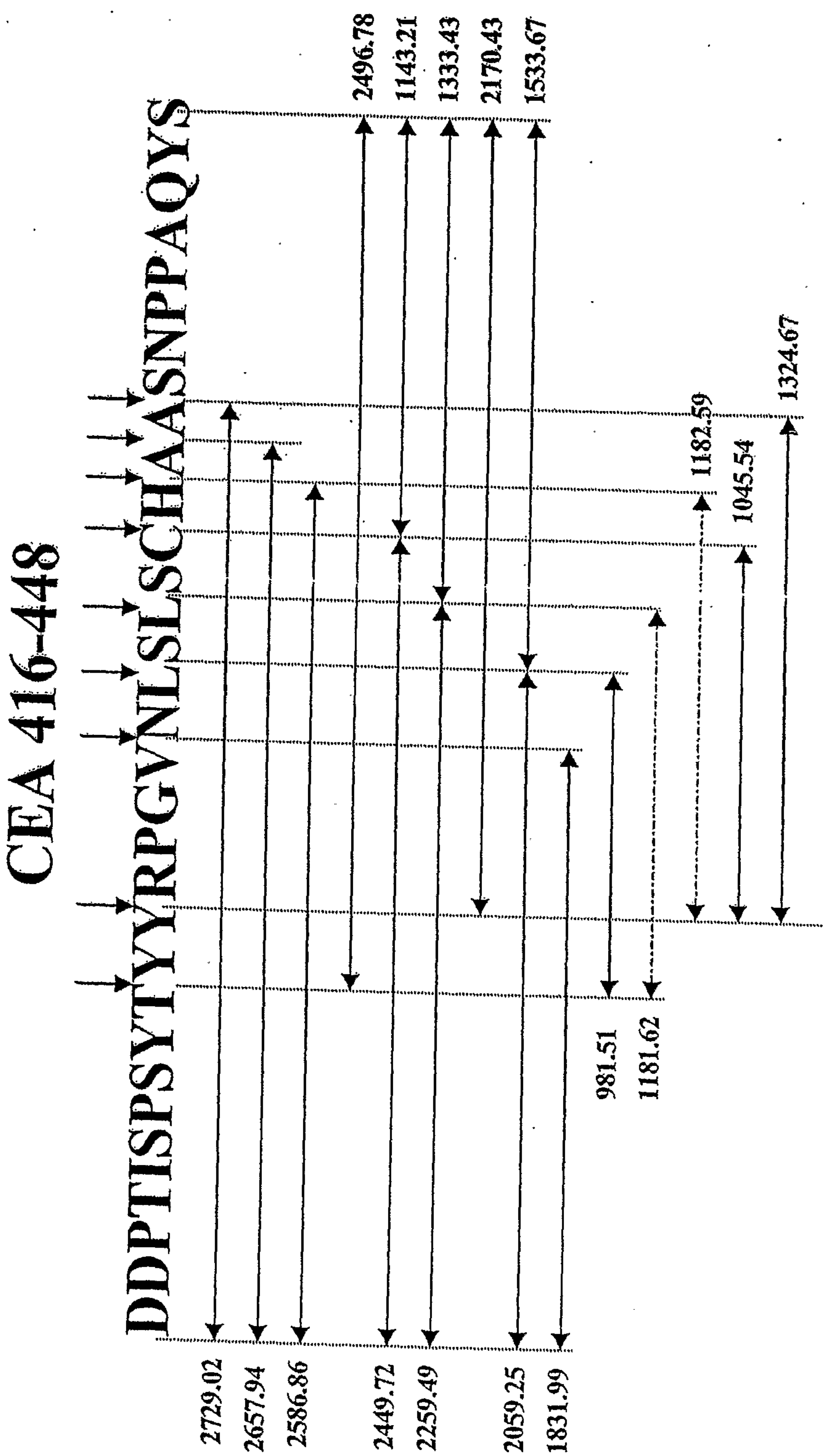

CEA 416-448
DDPTISPSYTYYRPGVNLSLSCHAASNPPAQYS
2496.78
1143.21
1333.43
2170.43
1533.67
1324.67
1182.59
1045.54
981.51
1181.62
2729.02
2657.94
2586.86
2449.72
2259.49
2059.25
1831.99

Figure 30

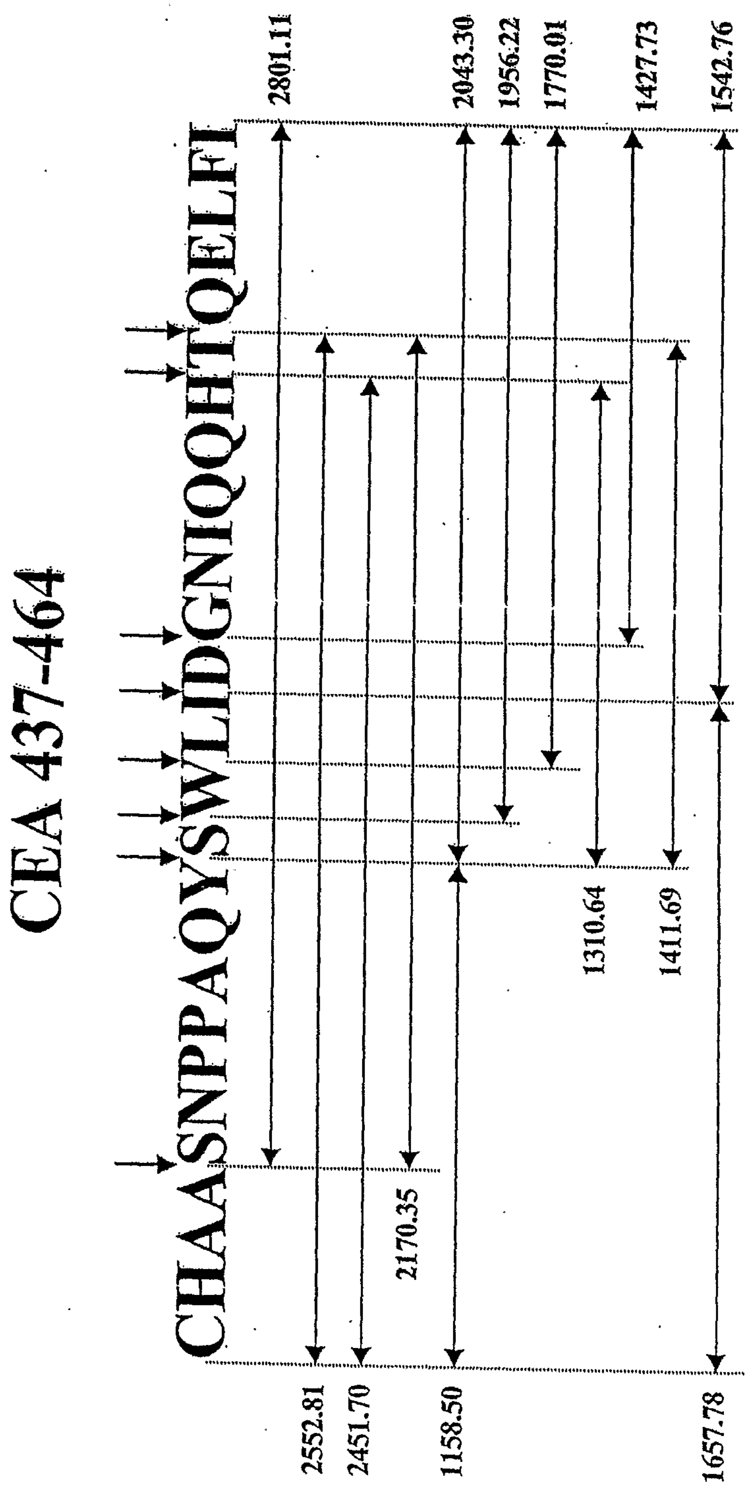

CEA 437-464
CHAAASNPPAQYSWLIDGNIQQHTQELFI
2801.11
2043.30
1956.22
1770.01
1427.73
1542.76
2552.81
2451.70
2170.35
1158.50
1310.64
1411.69
1657.78

Figure 31

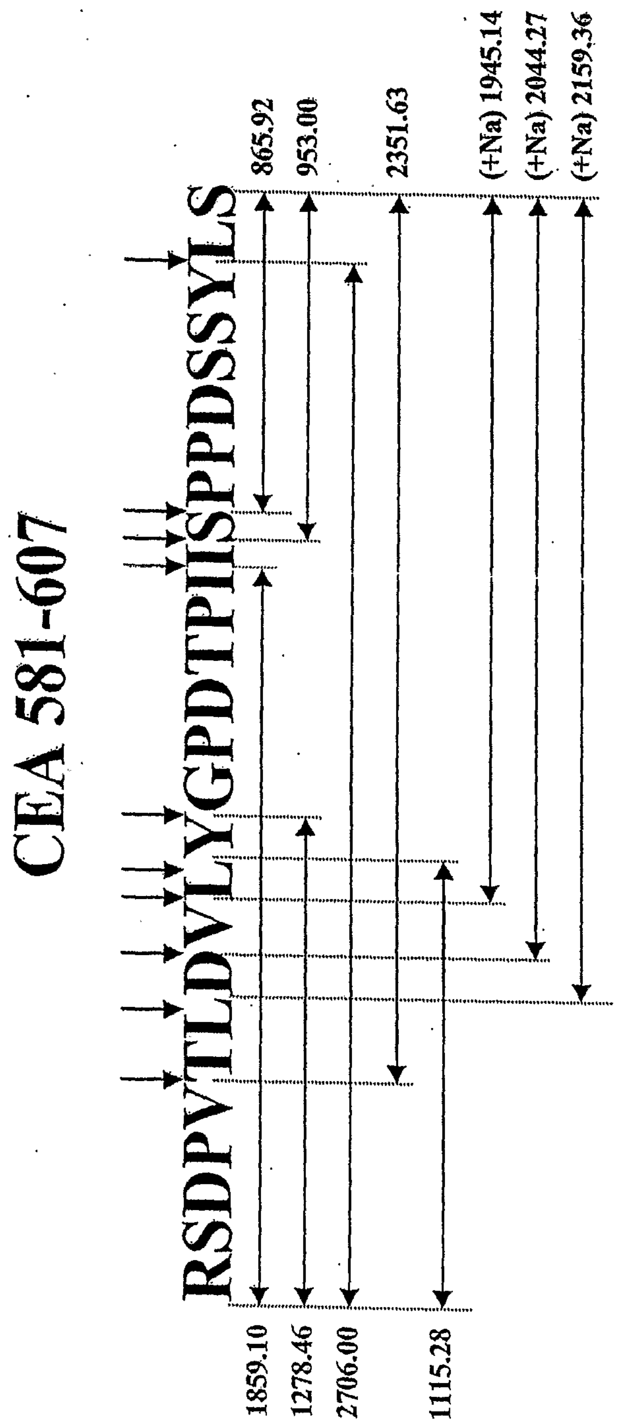

CEA 581-607
RSDPVTLDVLYGPDTPIISPPDSSYLS
865.92
953.00
2351.63
(+Na) 1945.14
(+Na) 2044.27
(+Na) 2159.36
1859.10
1278.46
2706.00
1115.28

Figure 32

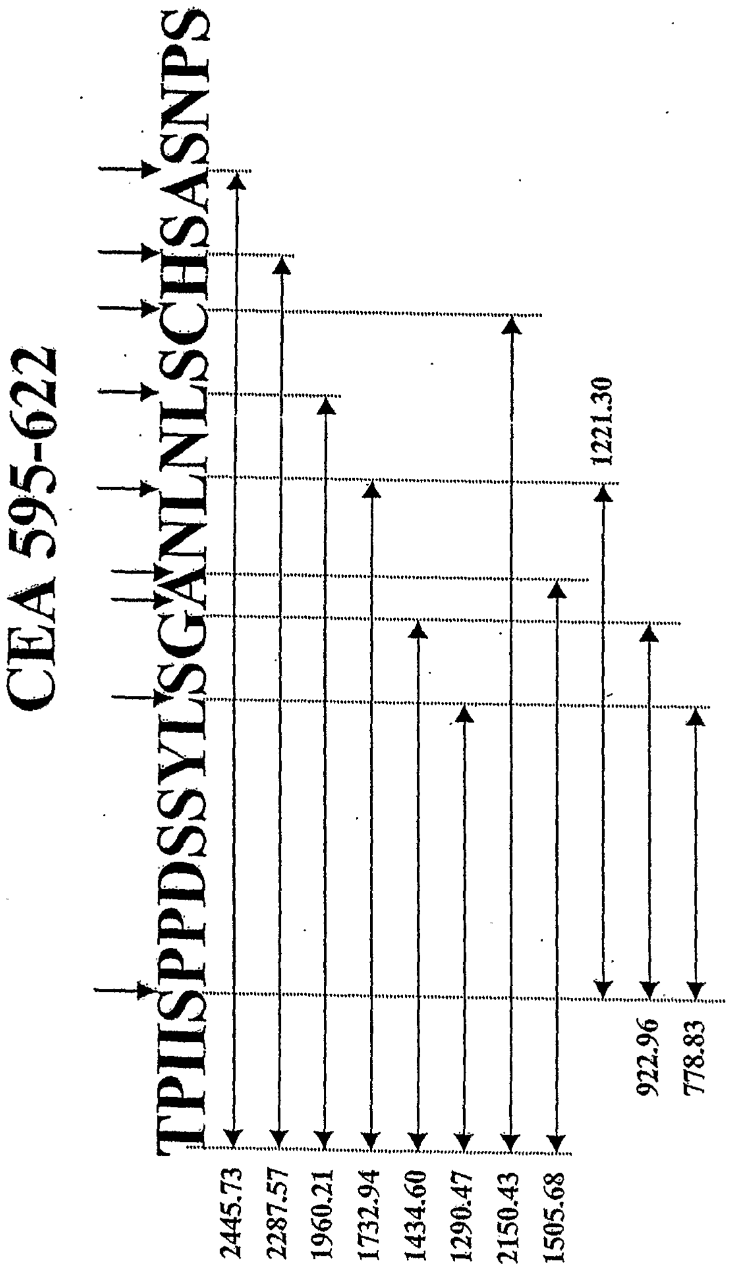

CEA 595-622
TPIISPPDSSYLSGANLNLSCHSASNPS
1221.30
922.96
778.83
2445.73
2287.57
1960.21
1732.94
1434.60
1290.47
2150.43
1505.68

Figure 33

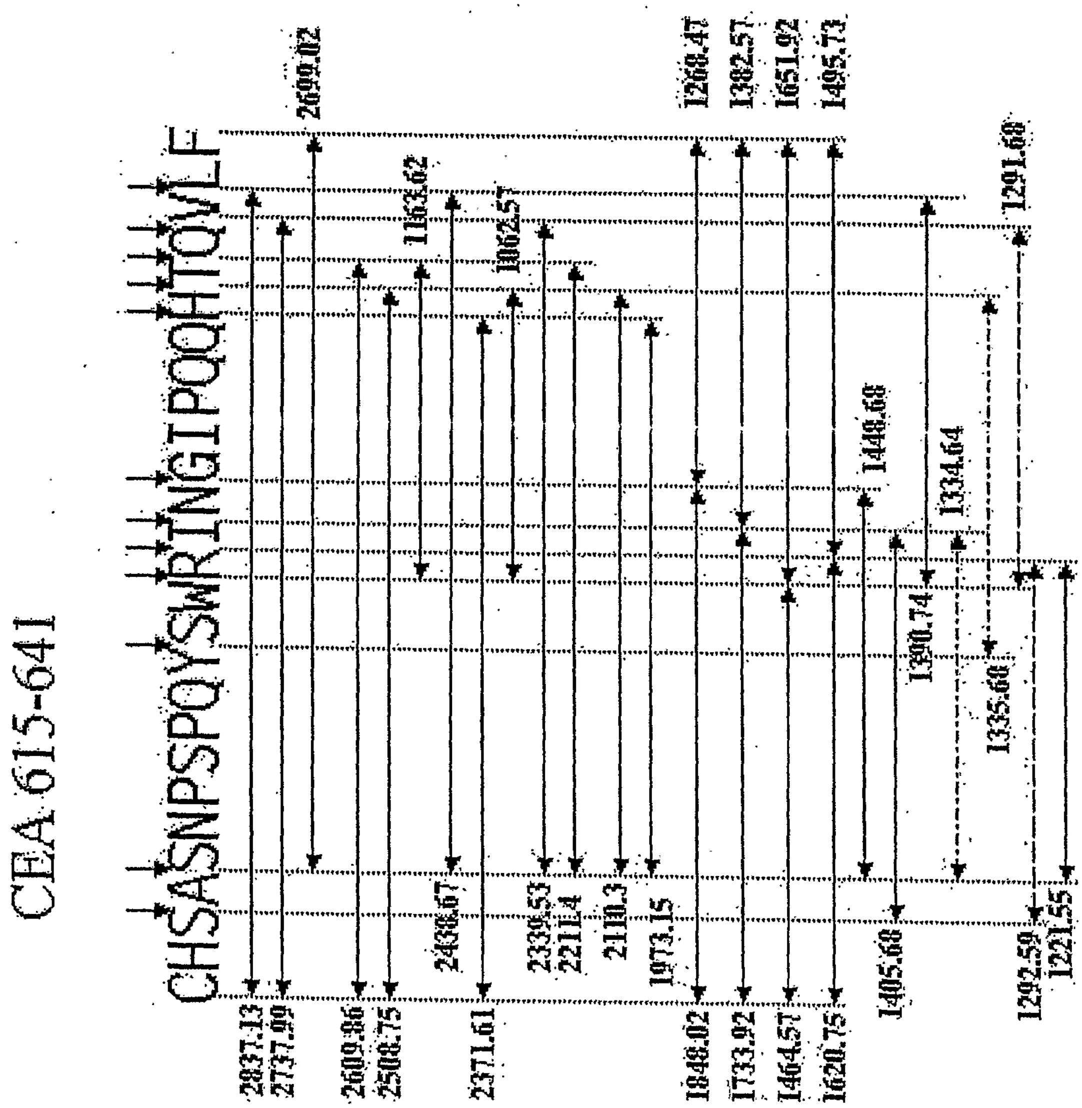

CEA 615-641
CHSASNPSPQYSWRINGIPQQHTQVLF
2837.13
2737.99
2699.02
2609.86
2508.75
2371.61
2438.67
1163.62
1062.57
2339.53
2211.4
2110.3
1973.15
1848.02
1268.47
1733.92
1382.57
1464.57
1651.92
1620.75
1495.73
1449.68
1405.68
1334.64
1390.74
1335.60
1291.60
1292.59
1221.55

Figure 34

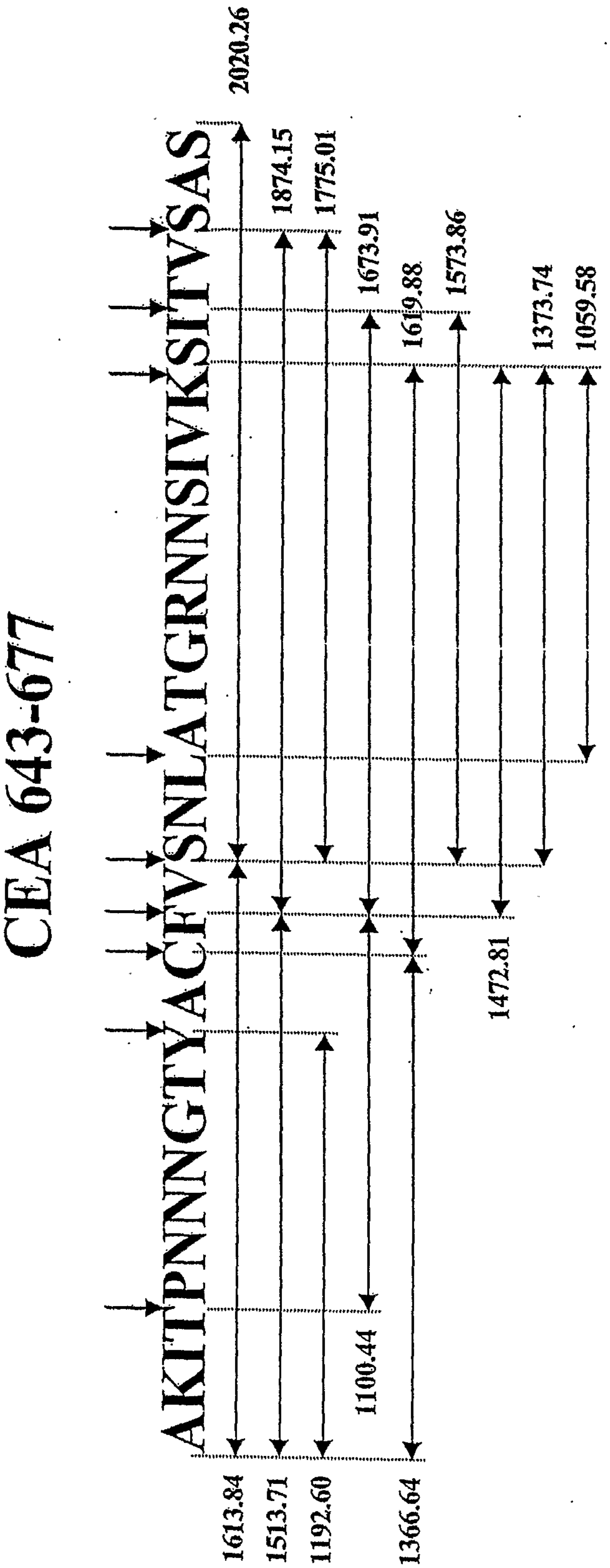

CEA 643-677
AKITPNNNGTYACFVSNLATGRNNNSIVKSITVSAS
2020.26
1874.15
1775.01
1673.91
1619.88
1573.86
1373.74
1059.58
1472.81
1100.44
1613.84
1513.71
1192.60
1366.64

Figure 35

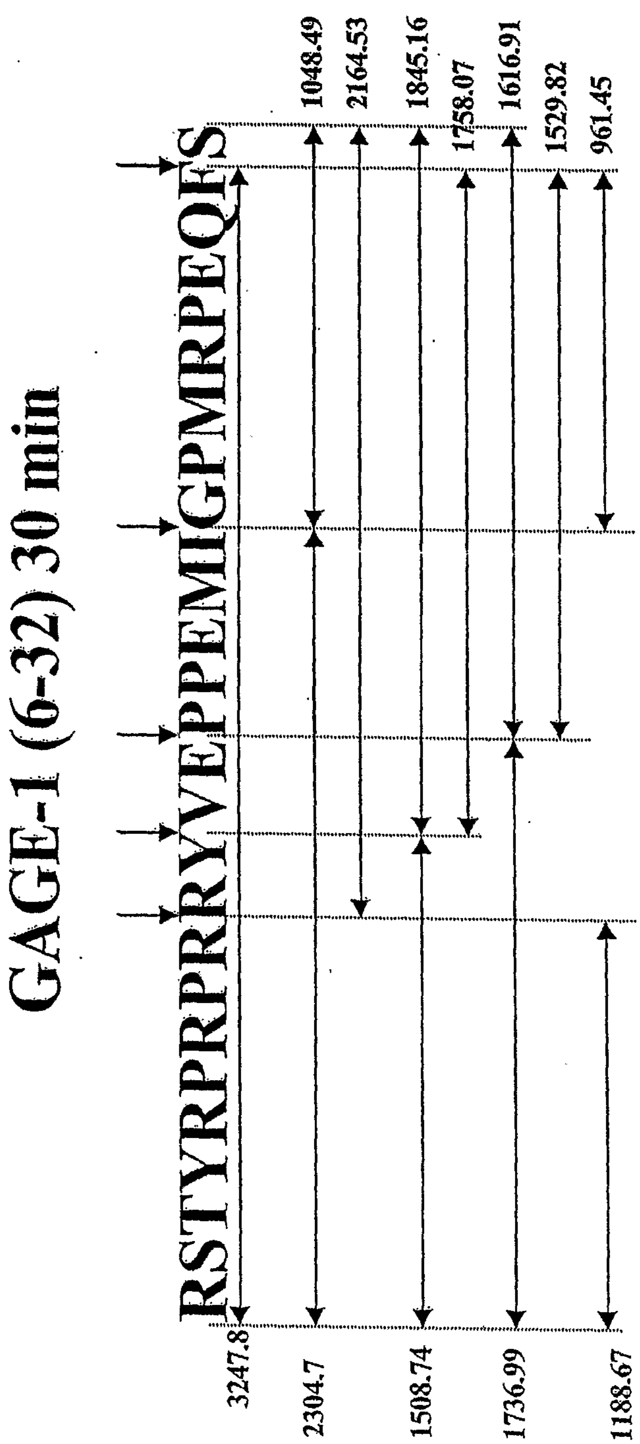

GAGE-1 (6-32) 30 min
RSTYRPRPRRYVEPPEMIGPMRPEQFS
1048.49
2164.53
1845.16
1758.07
1616.91
1529.82
961.45
3247.8
2304.7
1508.74
1736.99
1188.67

Figure 36

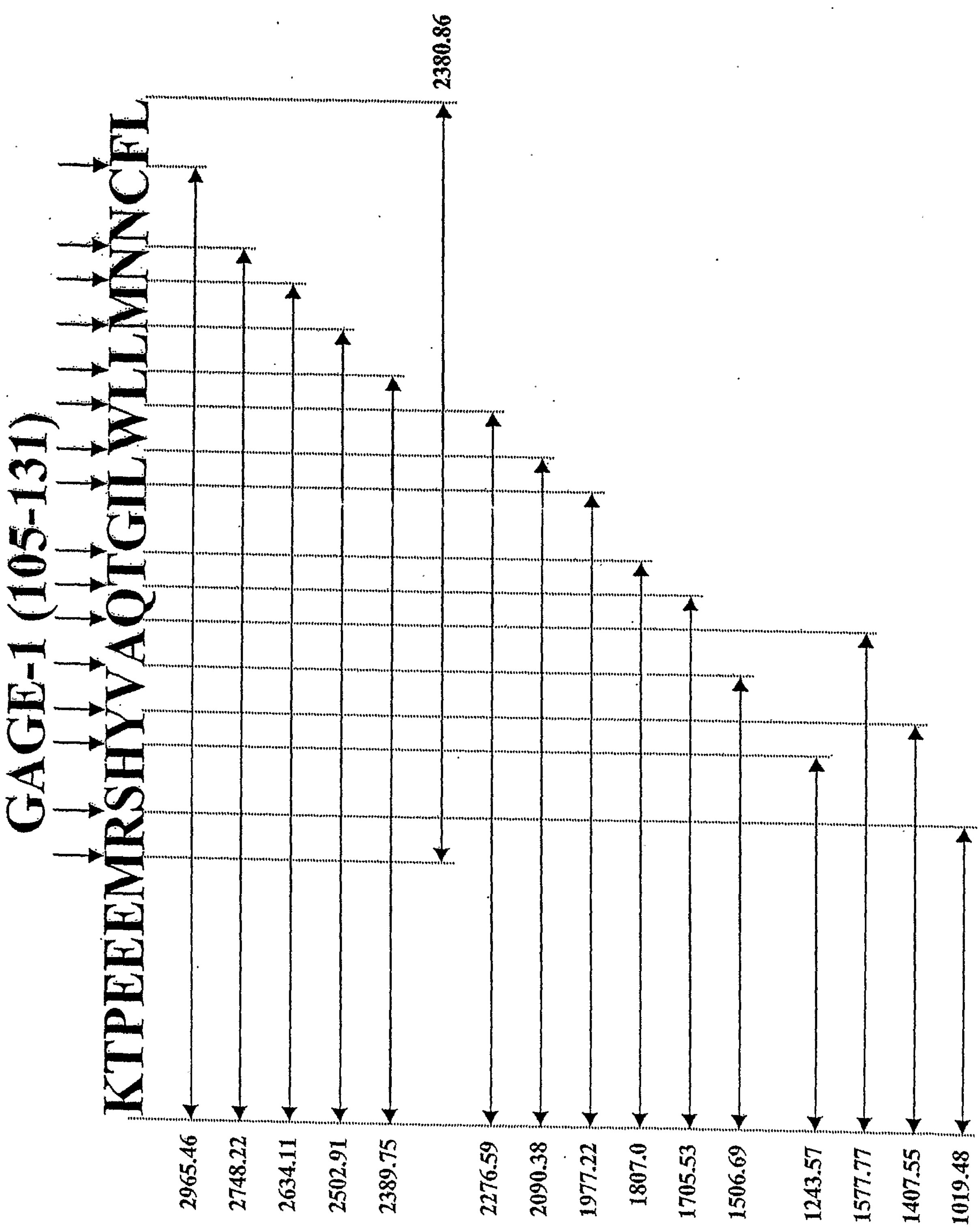

GAGE-1 (105-131)
KTPEEEMRSHYVAQTGILWLLMNNCFL
2380.86
2965.46
2748.22
2634.11
2502.91
2389.75
2276.59
2090.38
1977.22
1807.0
1705.53
1506.69
1243.57
1577.77
1407.55
1019.48

Figure 37

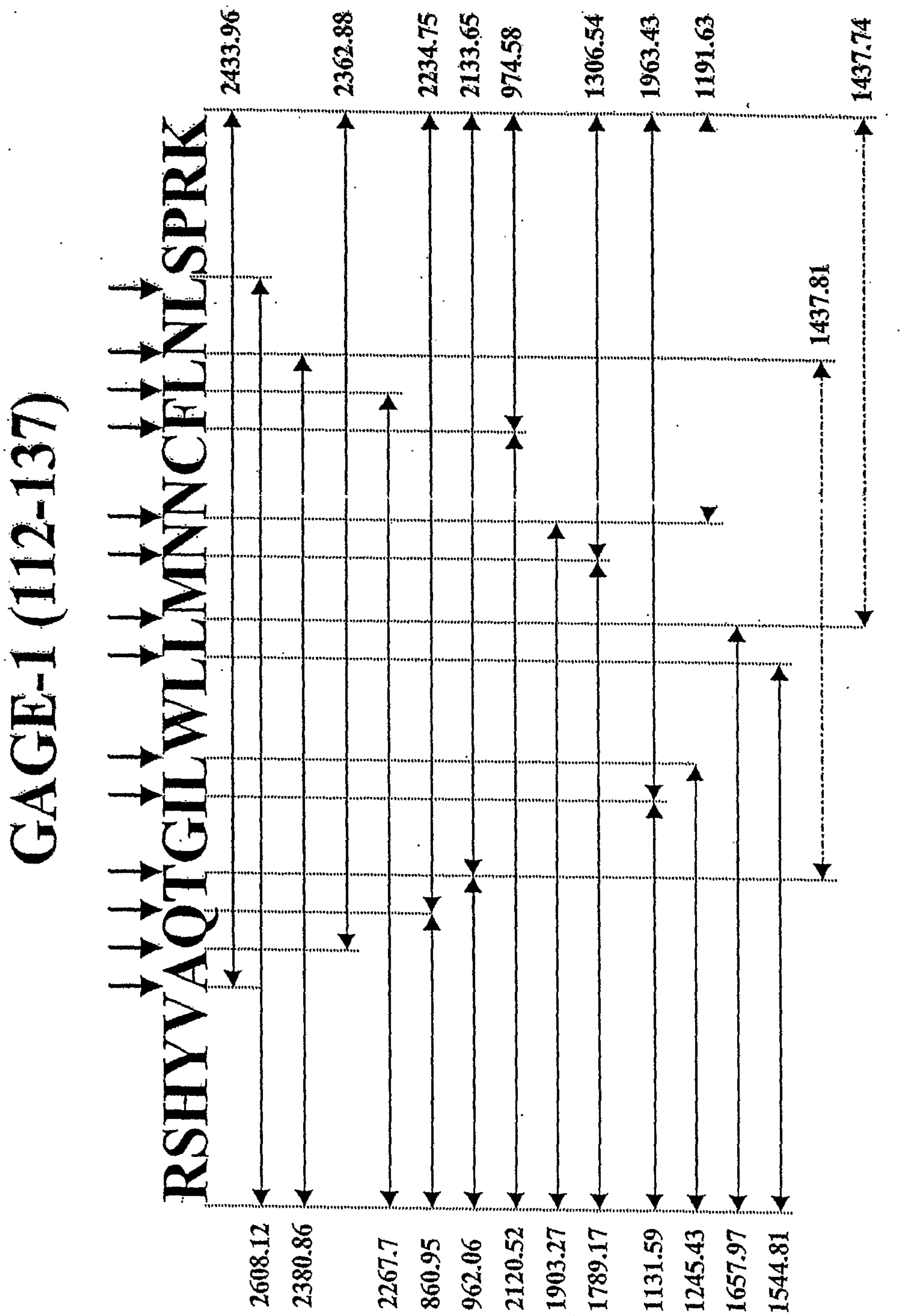

GAGE-1 (112-137)
RSHYVAQTGILWLLMNNCFLNLSPRK
2433.96
2362.88
2234.75
2133.65
974.58
1306.54
1963.43
1191.63
1437.74
1437.81
2608.12
2380.86
2267.7
860.95
962.06
2120.52
1903.27
1789.17
1131.59
1245.43
1657.97
1544.81

Figure 38

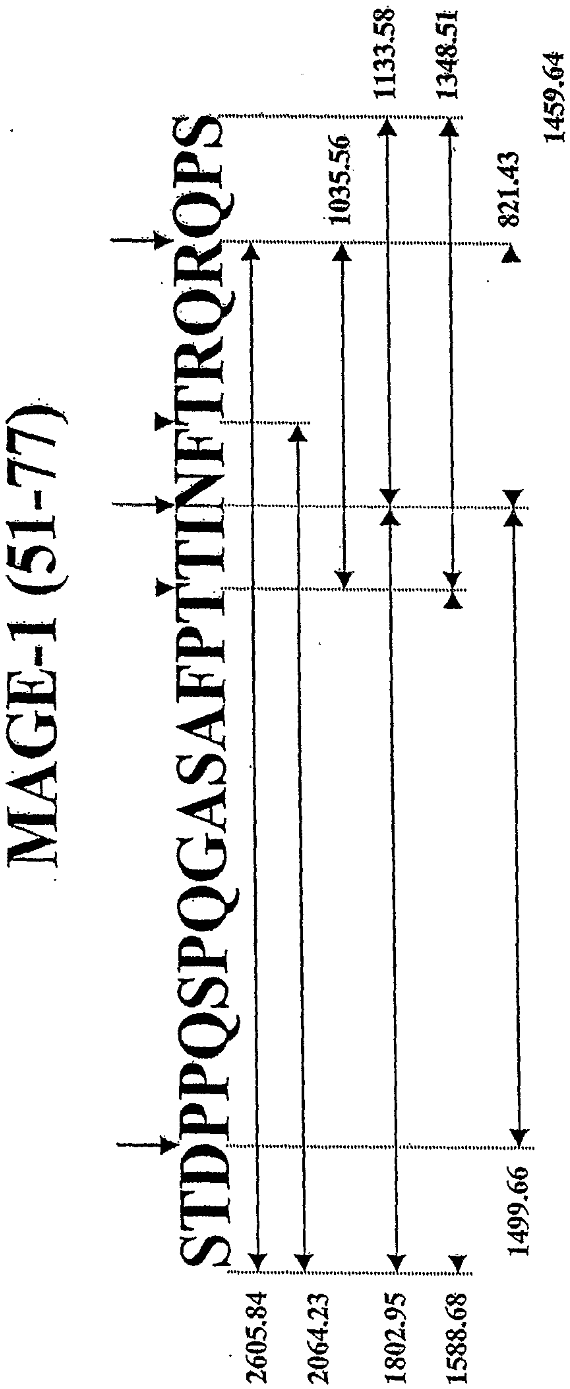

MAGE-1 (51-77)
STDPPQSPQGASAFPTTINFTRQRQPS
2605.84
2064.23
1802.95
1588.68
1499.66
1035.56
1133.58
1348.51
821.43
1459.64

Figure 39

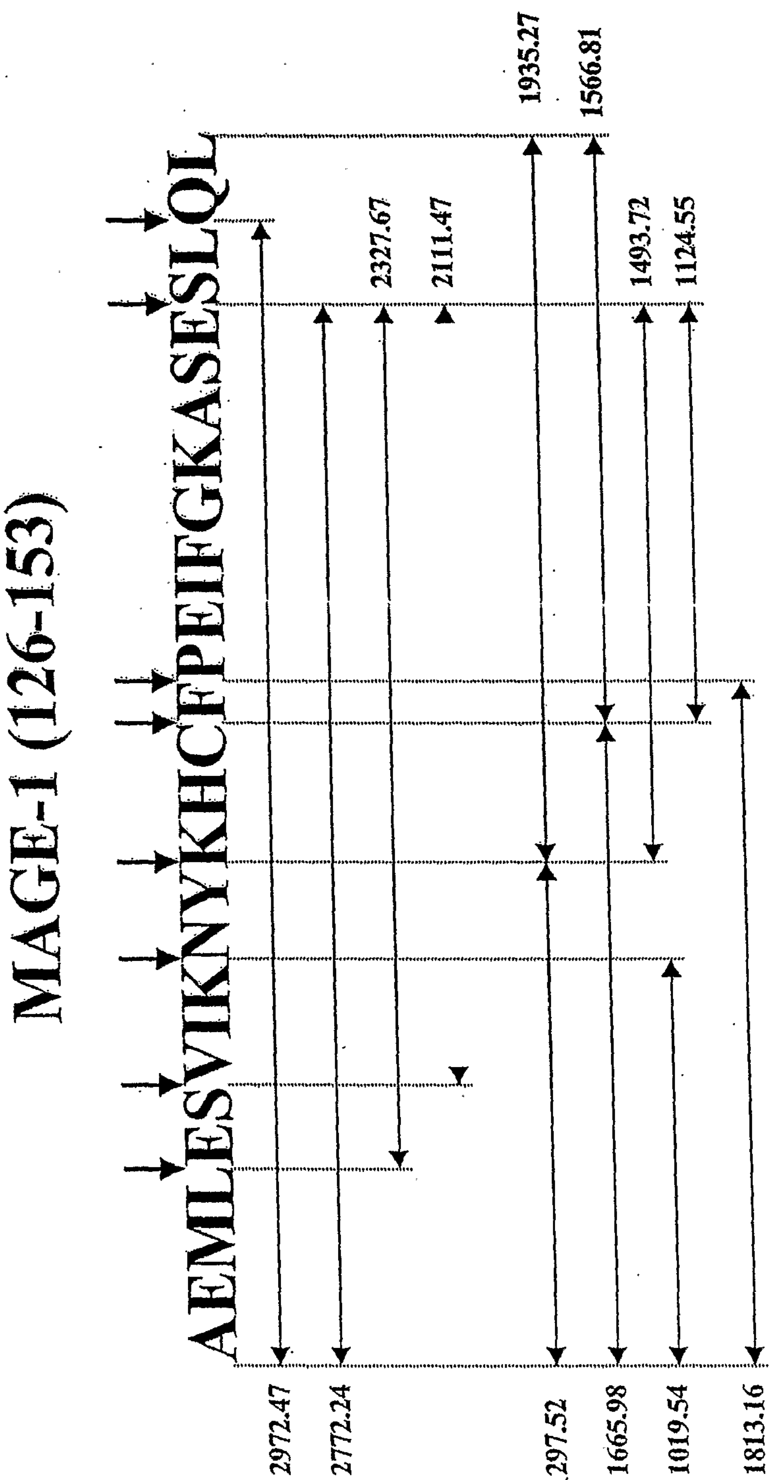

MAGE-1 (126-153)
AEMILESVIKNYKHCFPEIFGKASESLQL
1935.27
1566.81
2327.67
2111.47
1493.72
1124.55
2972.47
2772.24
1297.52
1665.98
1019.54
1813.16

Figure 40

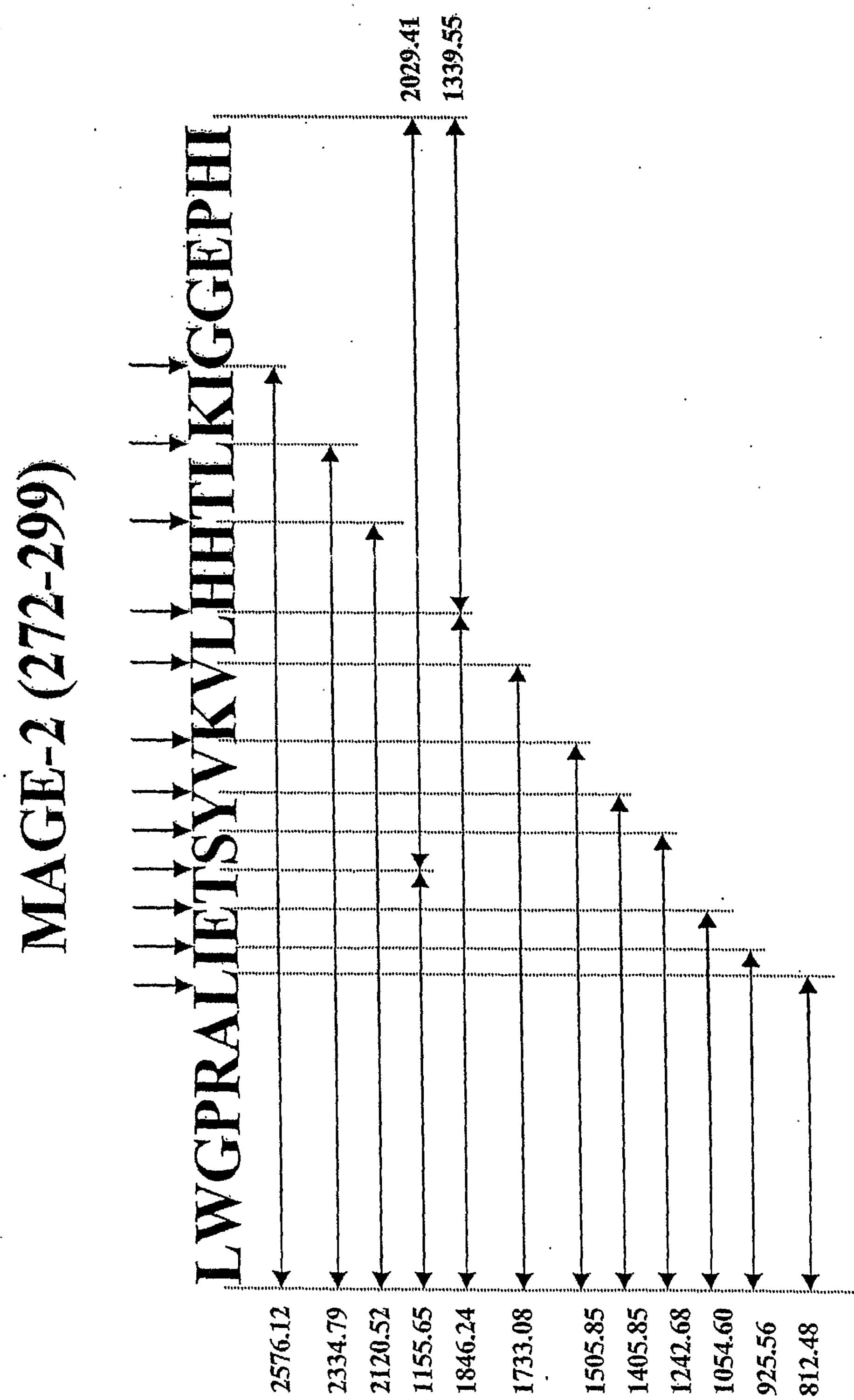

MAGE-2 (272-299)
LWGPRALIETSYVKVLHHTLKIGGEPHI
2029.41
1339.55
2576.12
2334.79
2120.52
1155.65
1846.24
1733.08
1505.85
1405.85
1242.68
1054.60
925.56
812.48

Figure 41

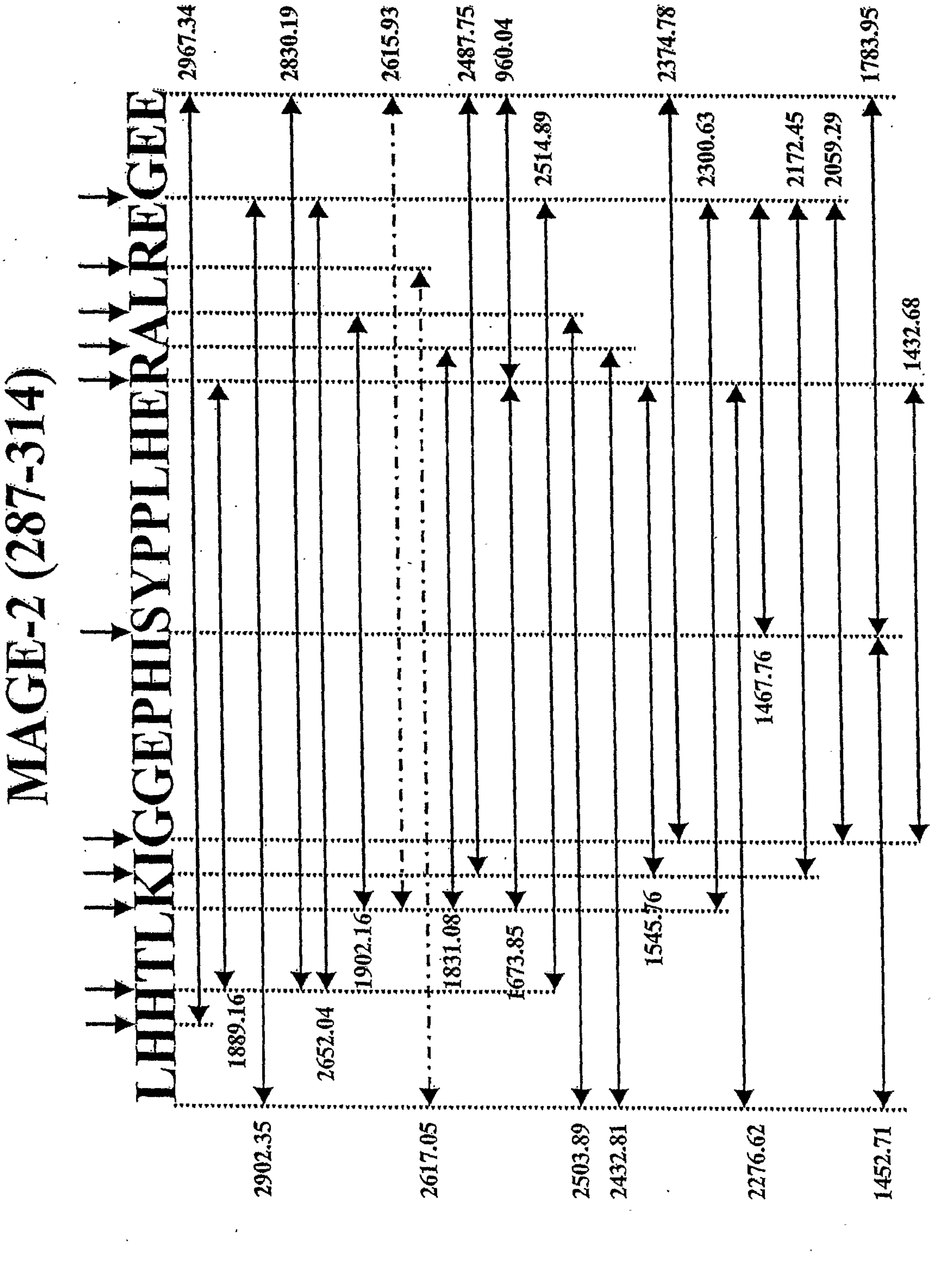

MAGE-2 (287-314)
LHHTLKIGGGEPHISYPPLHERALREGEE
2967.34
2830.19
2615.93
2487.75
960.04
2374.78
1783.95
2514.89
2300.63
2172.45
2059.29
1432.68
1467.76
1889.16
2652.04
1902.16
1831.08
1673.85
1545.76
2902.35
2617.05
2503.89
2432.81
2276.62
1452.71

Figure 42

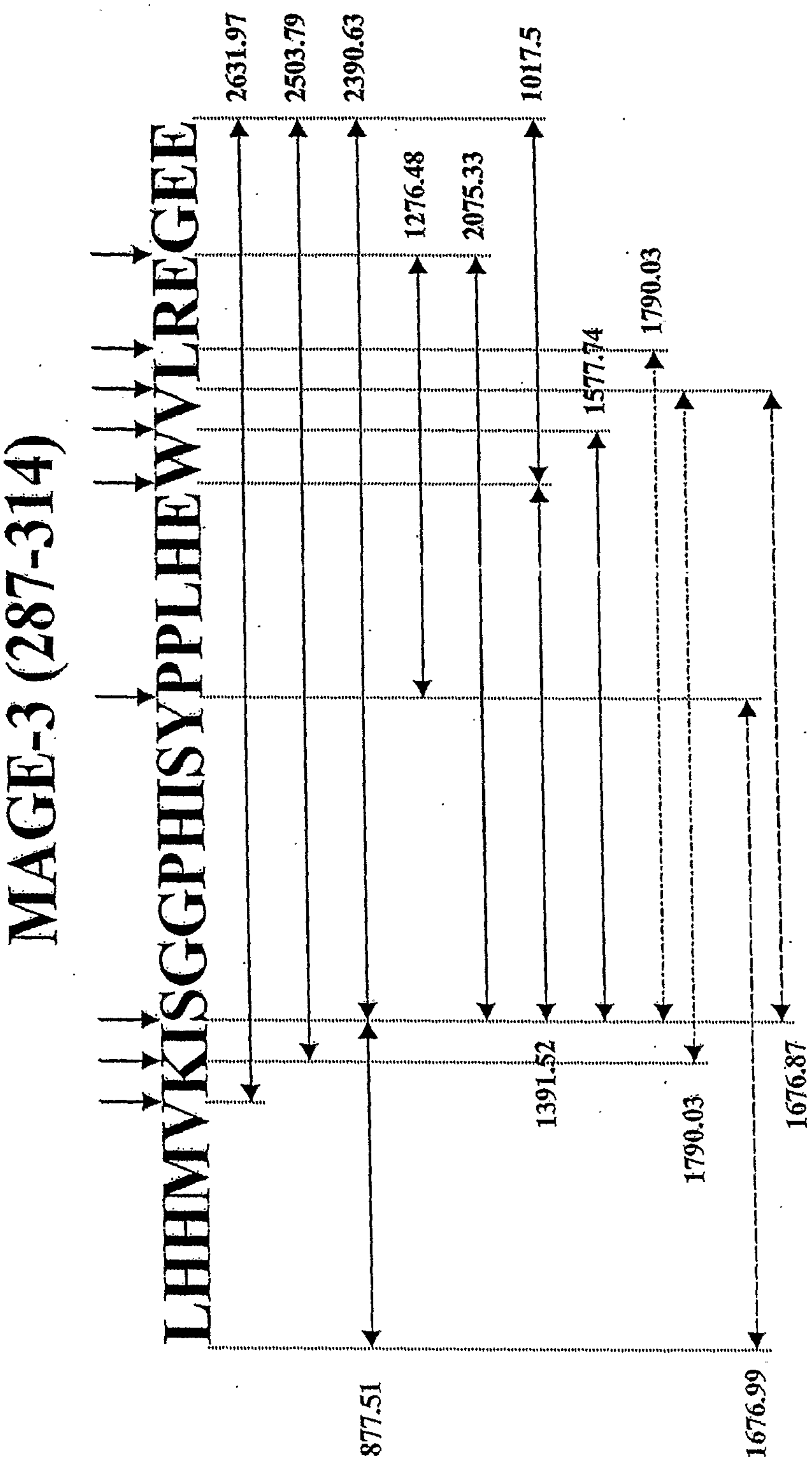

MAGE-3 (287-314)
LHHMVKISGGPHISYPPLHEWVLREGEE
2631.97
2503.79
2390.63
1017.5
1276.48
2075.33
1790.03
1577.74
877.51
1391.52
1790.03
1676.87
1676.99

Figure 43

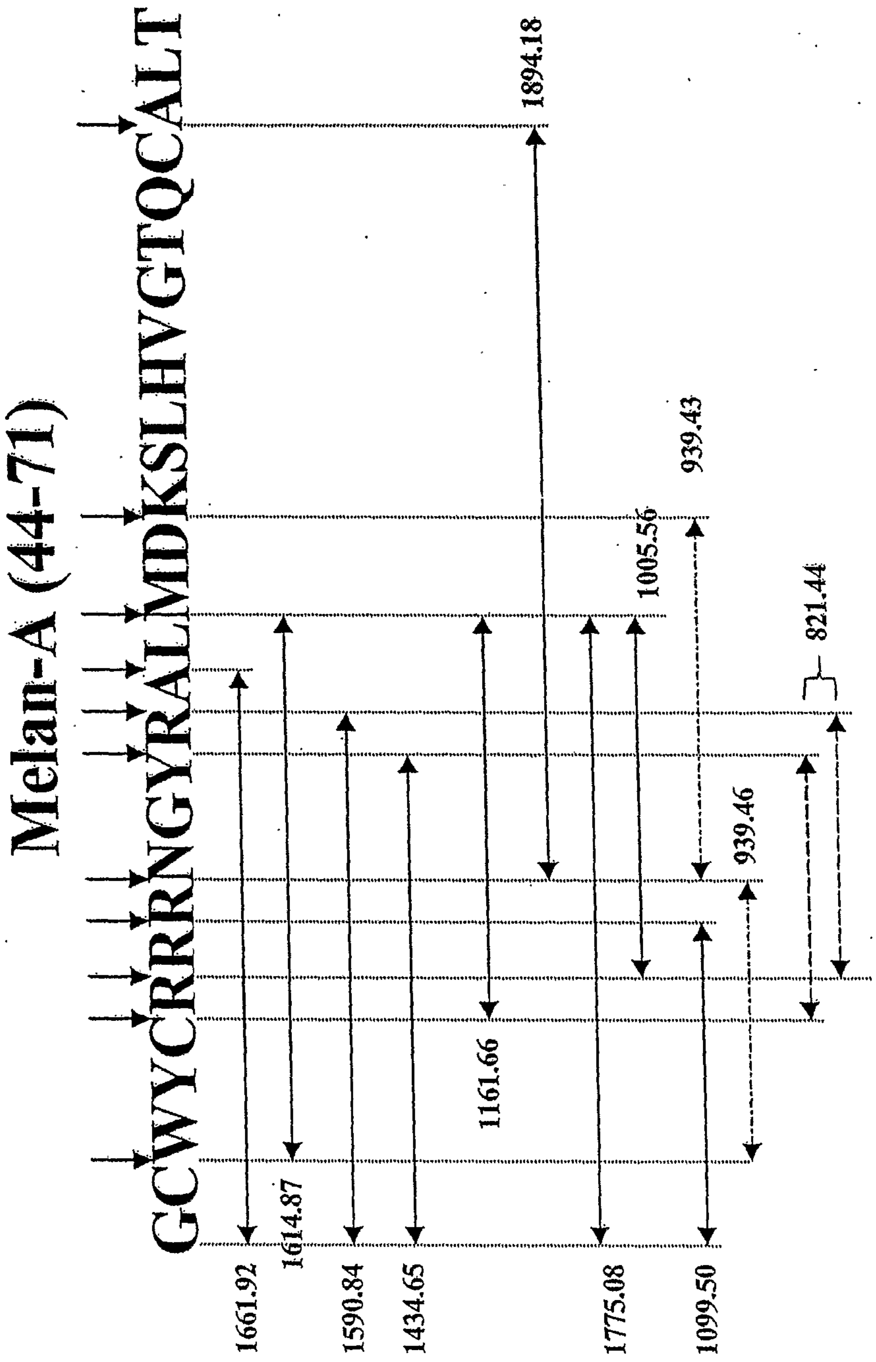

Melan-A (44-71)
GCWYCRRRNGYRALMDKSLHVGTQCALT
1894.18
939.43
1005.56
821.44
939.46
1161.66
1614.87
1661.92
1590.84
1434.65
1775.08
1099.50

Figure 44

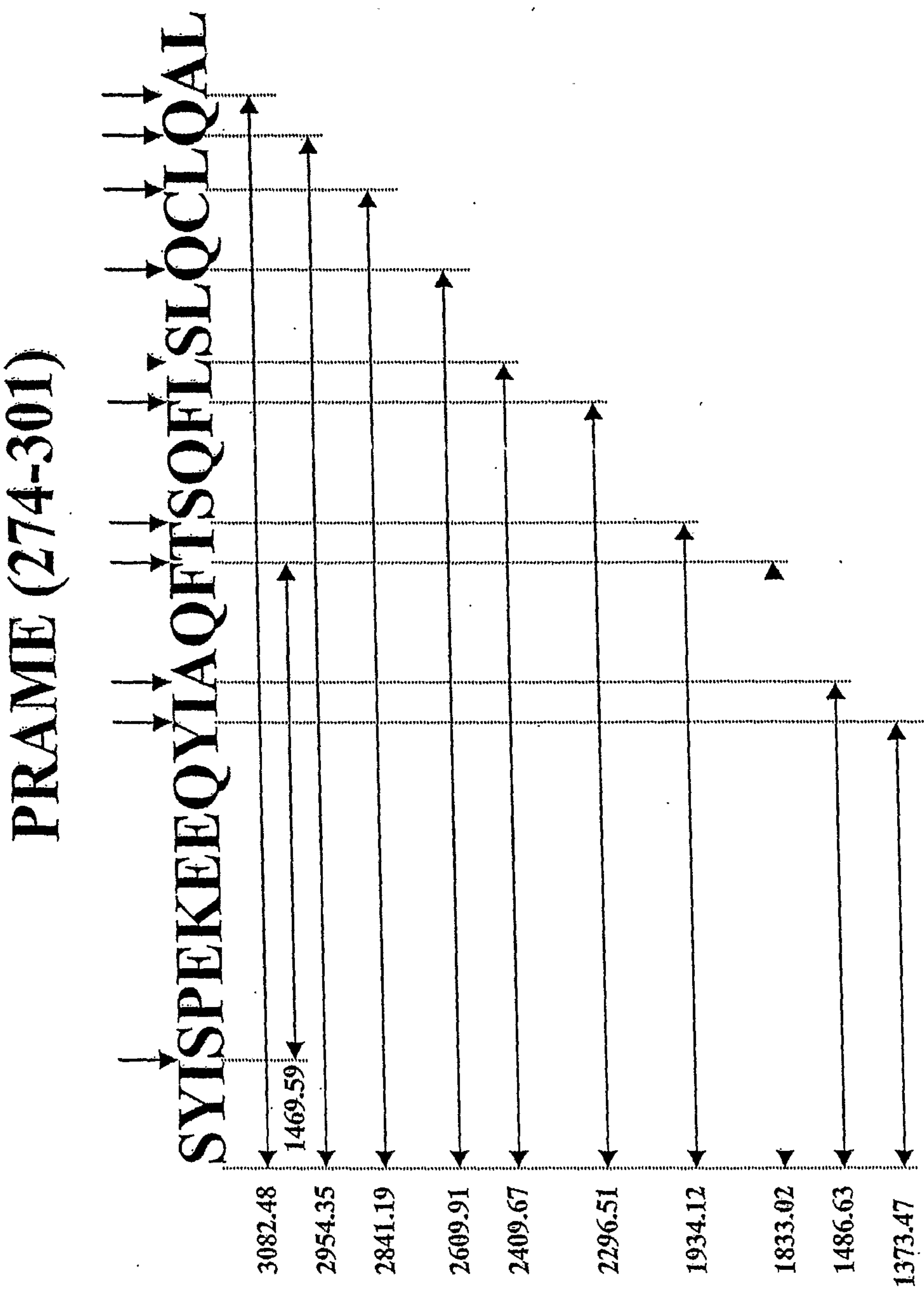

PRAME (274-301)
SYISPEKEEQYIAQFTSQFLSLQCLQAL
1469.59
3082.48
2954.35
2841.19
2609.91
2409.67
2296.51
1934.12
1833.02
1486.63
1373.47

Figure 45

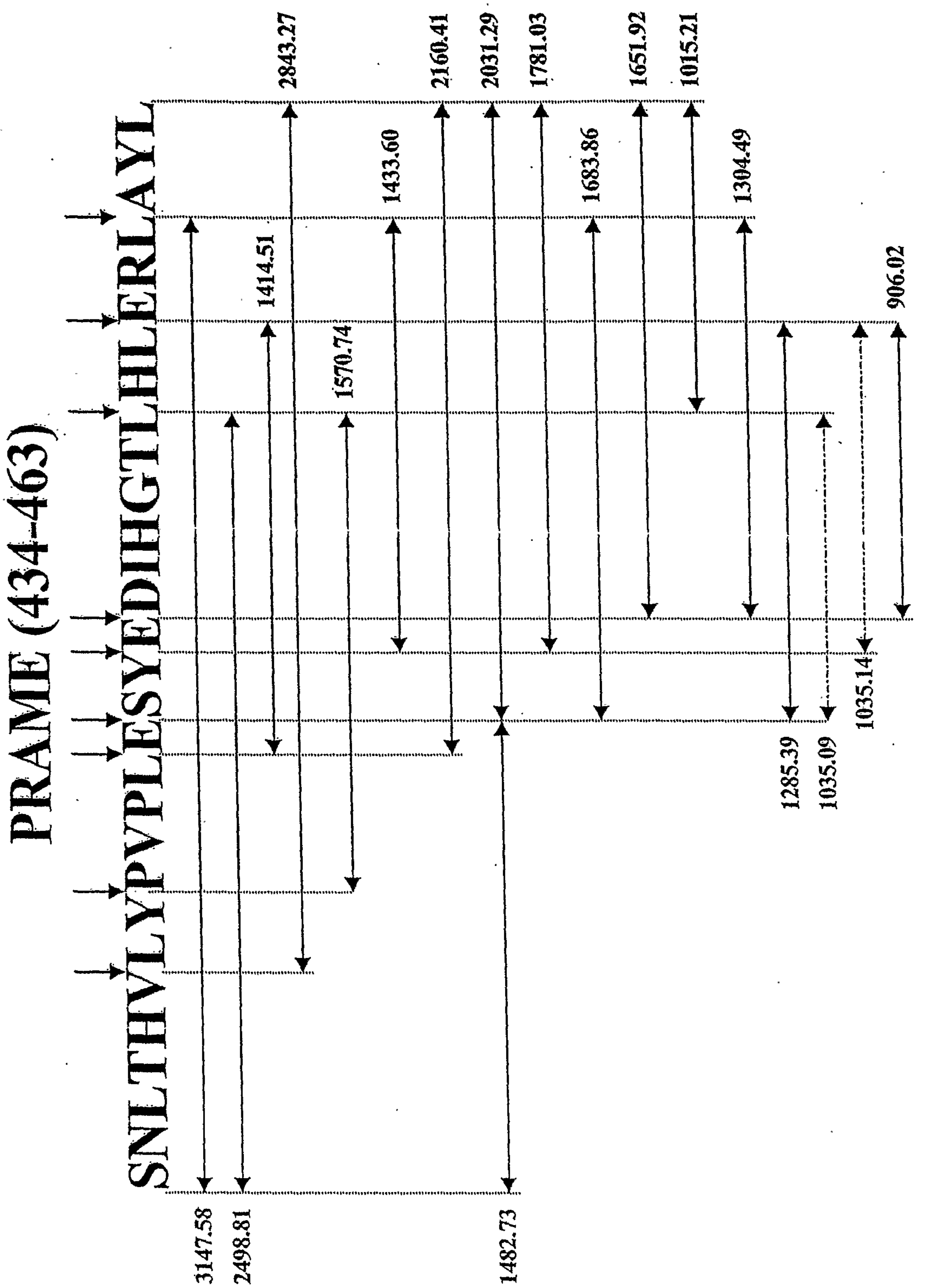

PRAME (434-463)
SNLTHVLYPVPLESYEDIHGTLHLERLAYL
2843.27
2160.41
2031.29
1781.03
1651.92
1015.21
1433.60
1683.86
1304.49
1414.51
906.02
1570.74
1035.14
1285.39
1035.09
3147.58
2498.81
1482.73

Figure 46

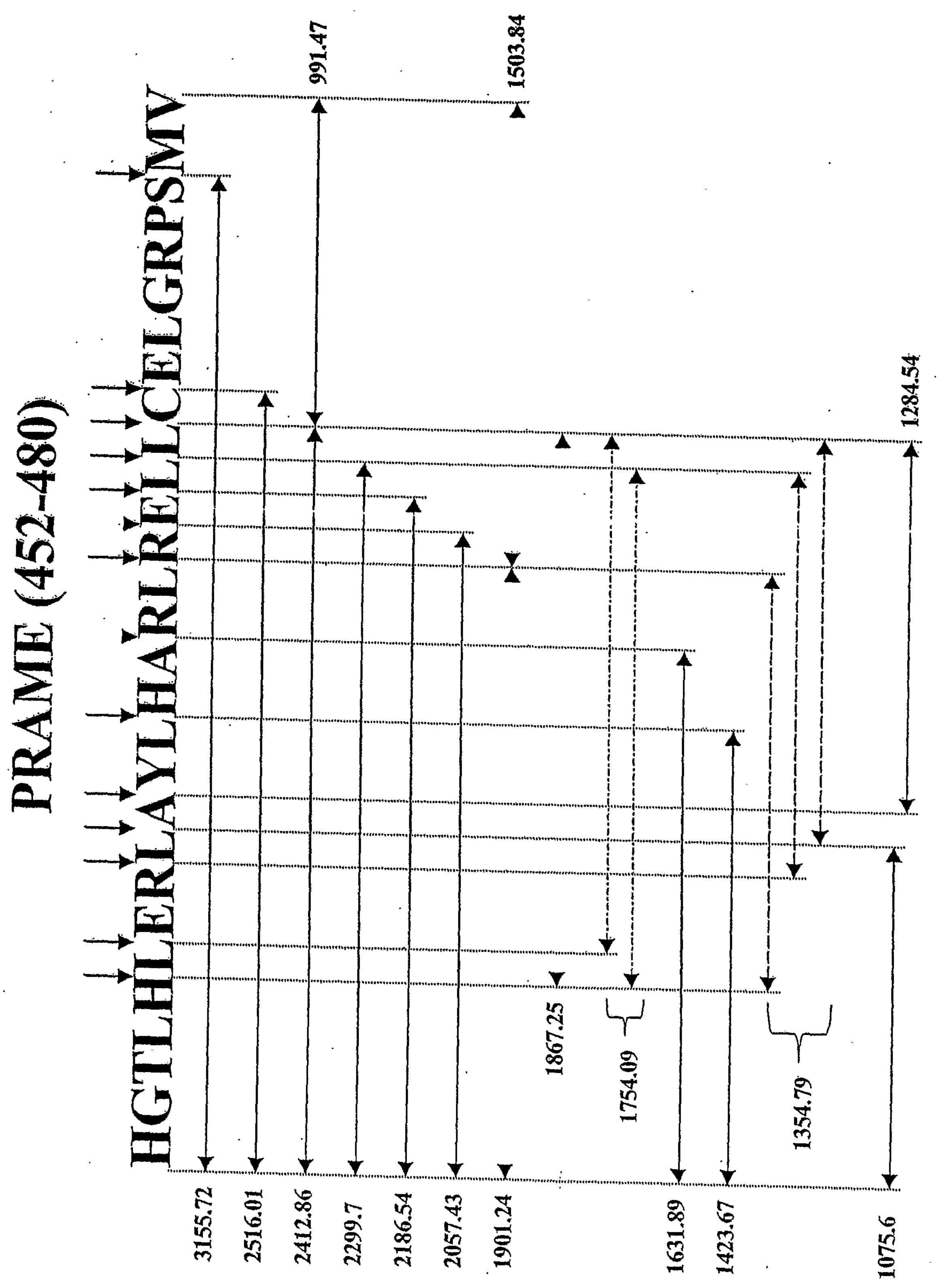

PRAME (452-480)
HGTLHLERLAYLHARLRELLCELGRPSMV
991.47
1503.84
1284.54
3155.72
2516.01
2412.86
2299.7
2186.54
2057.43
1901.24
1867.25
1754.09
1631.89
1423.67
1354.79
1075.6

Figure 47

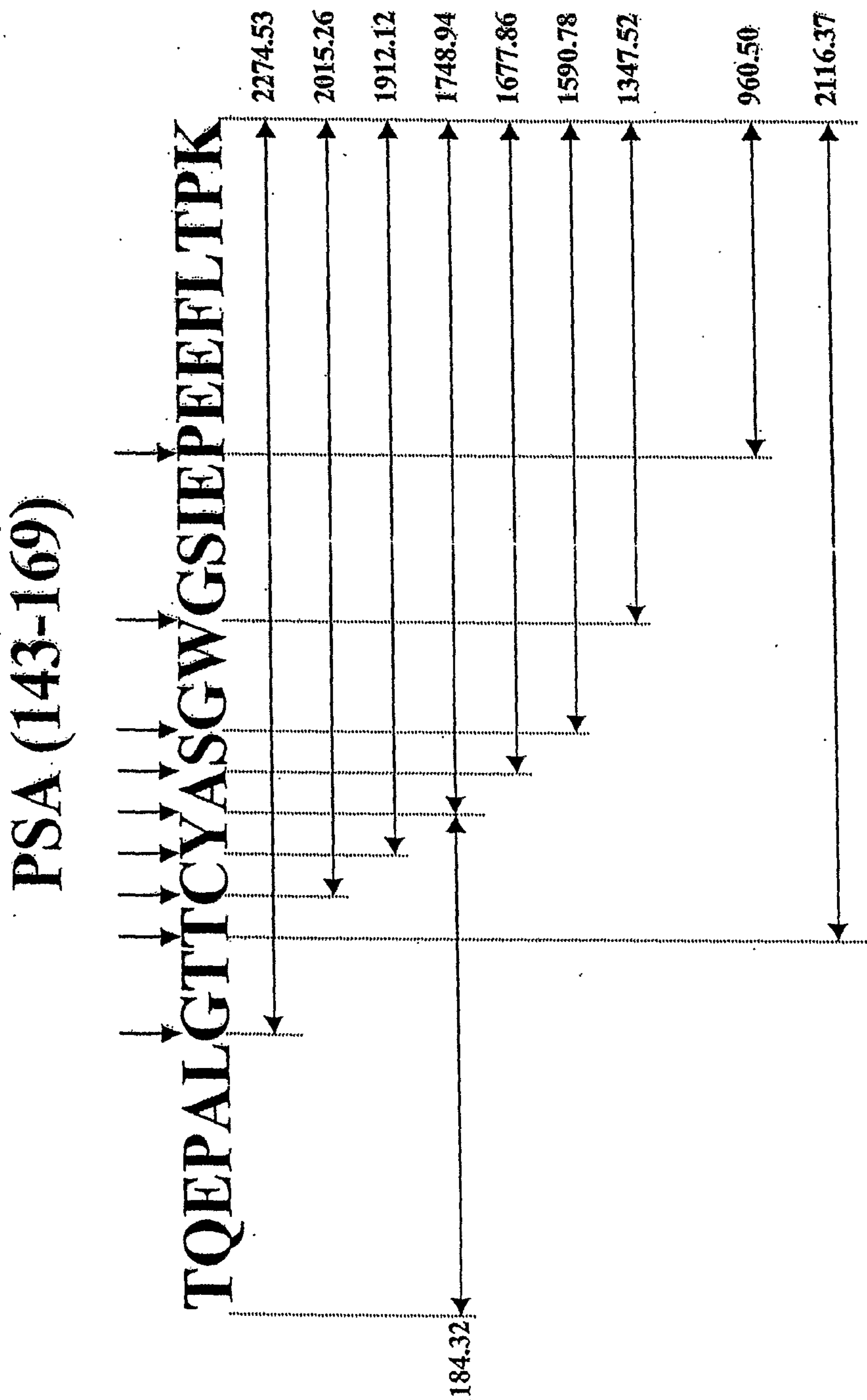

PSA (143-169)
TQEPALGTTCYASGWGSIEPEEFLTPK
2274.53
2015.26
1912.12
1748.94
1677.86
1590.78
1347.52
960.50
2116.37
1184.32

Figure 48

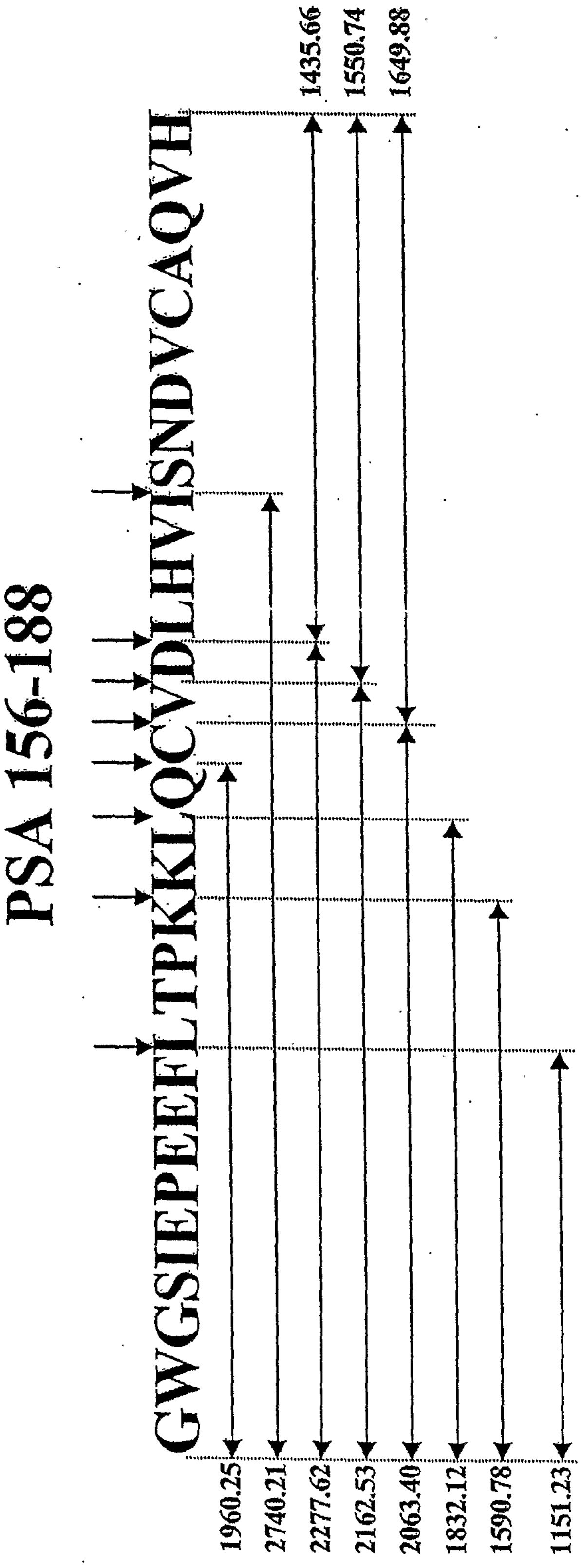

PSA 156-188
GWGSIEPEEFLTPKKLQCVDLHVISNDVCAQVH
1960.25
2740.21
2277.62
2162.53
2063.40
1832.12
1590.78
1151.23
1435.66
1550.74
1649.88

Figure 49

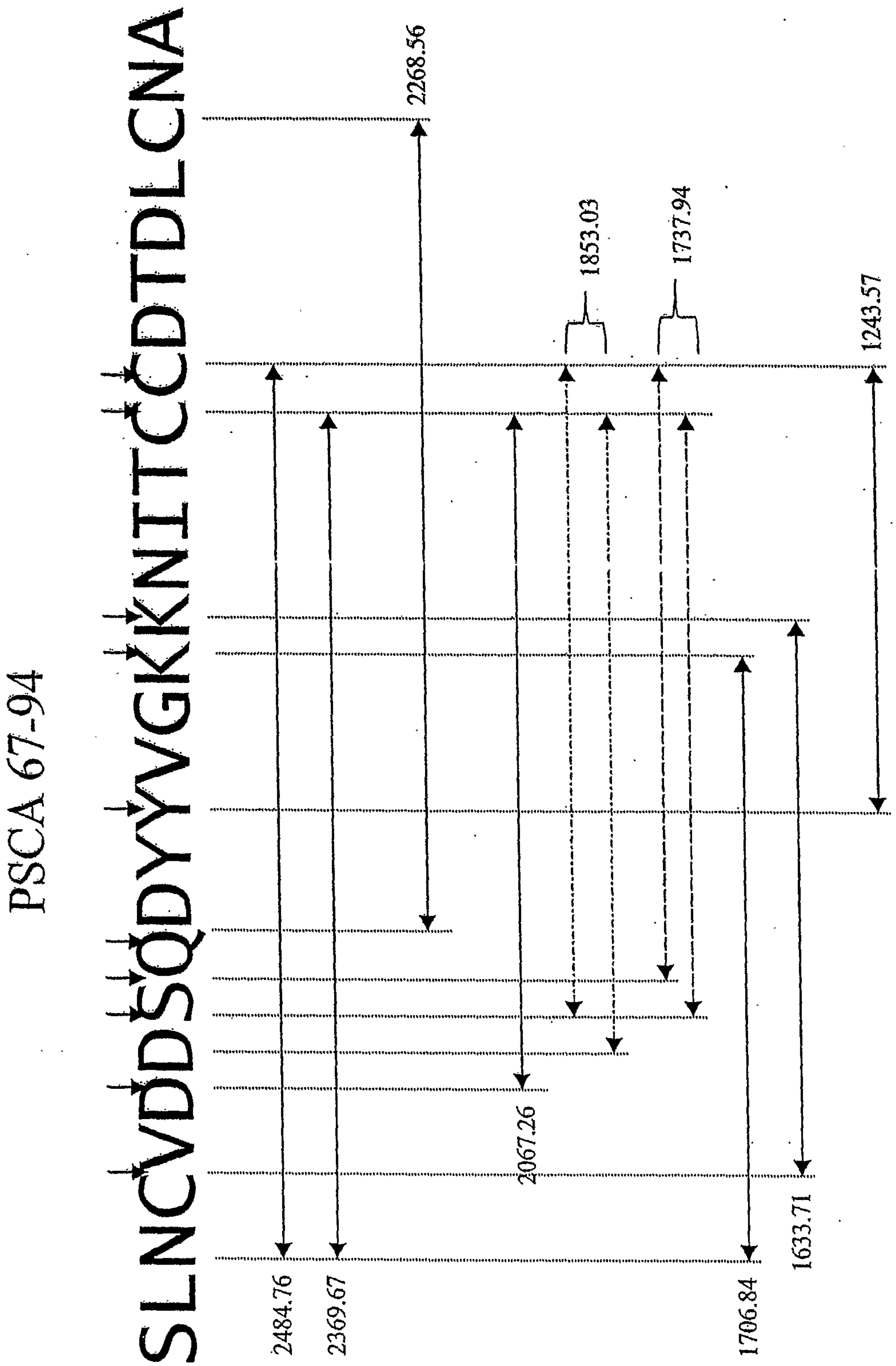

PSCA 67-94
SLNCVDDSQDYYVGKKNITCCDTDLCNA
2268.56
1853.03
1737.94
1243.57
2067.26
2484.76
2369.67
1706.84
1633.71

Figure 50

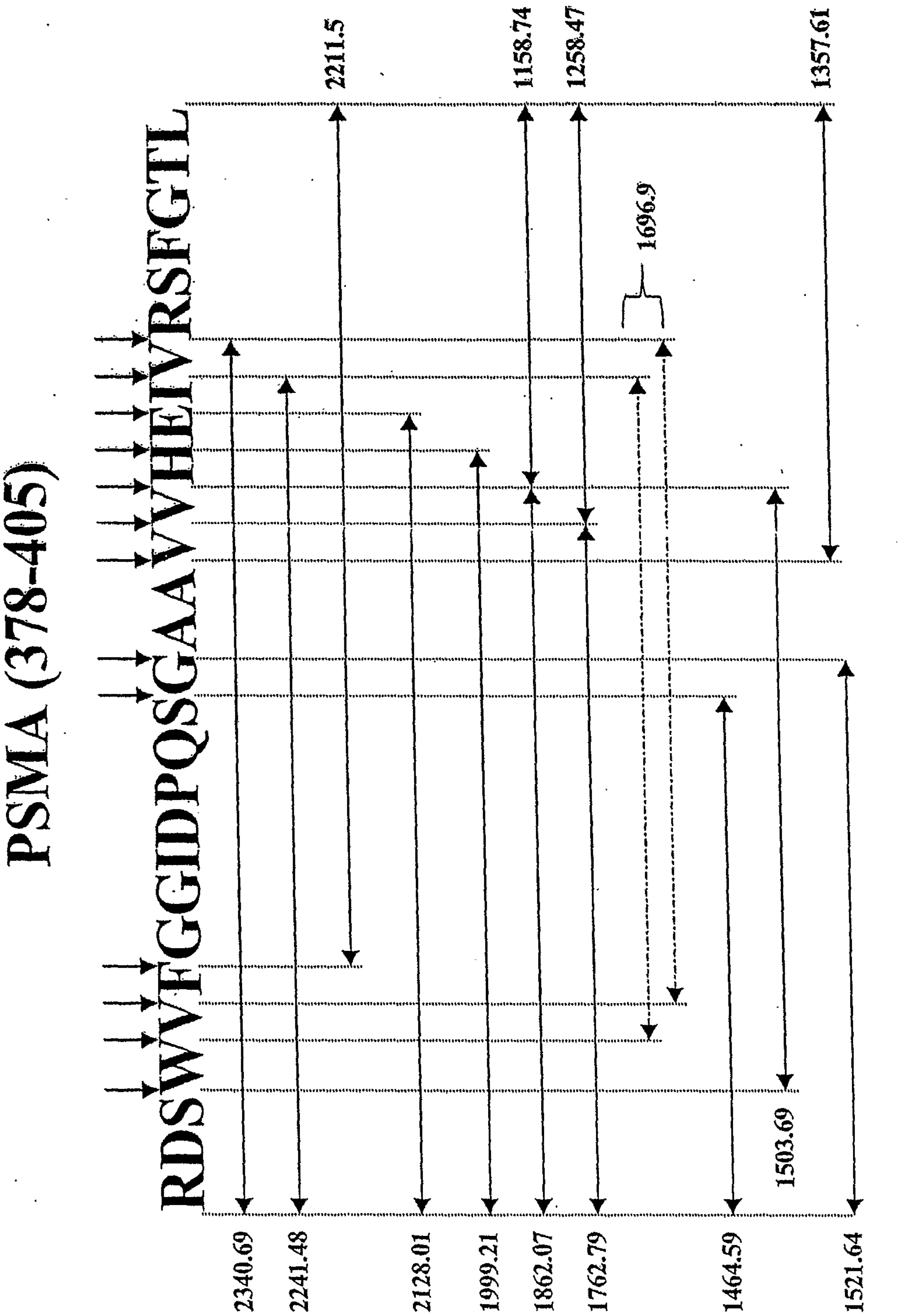

PSMA (378-405)
RDSWVFGGIDPQSGAAVVHEIVRSFGTL
2211.5
1158.74
1258.47
1357.61
1696.9
1503.69
2340.69
2241.48
2128.01
1999.21
1862.07
1762.79
1464.59
1521.64

Figure 51

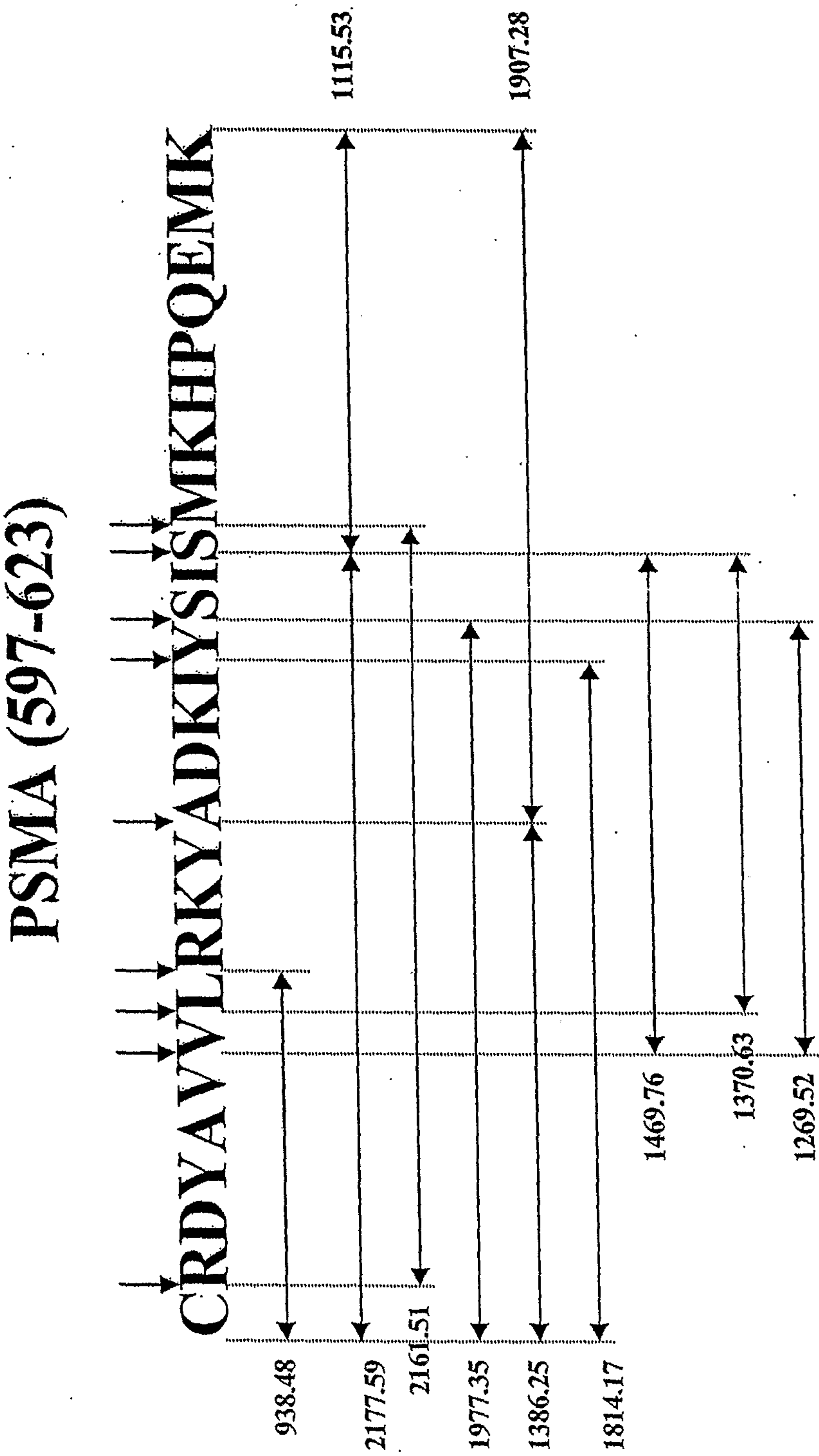
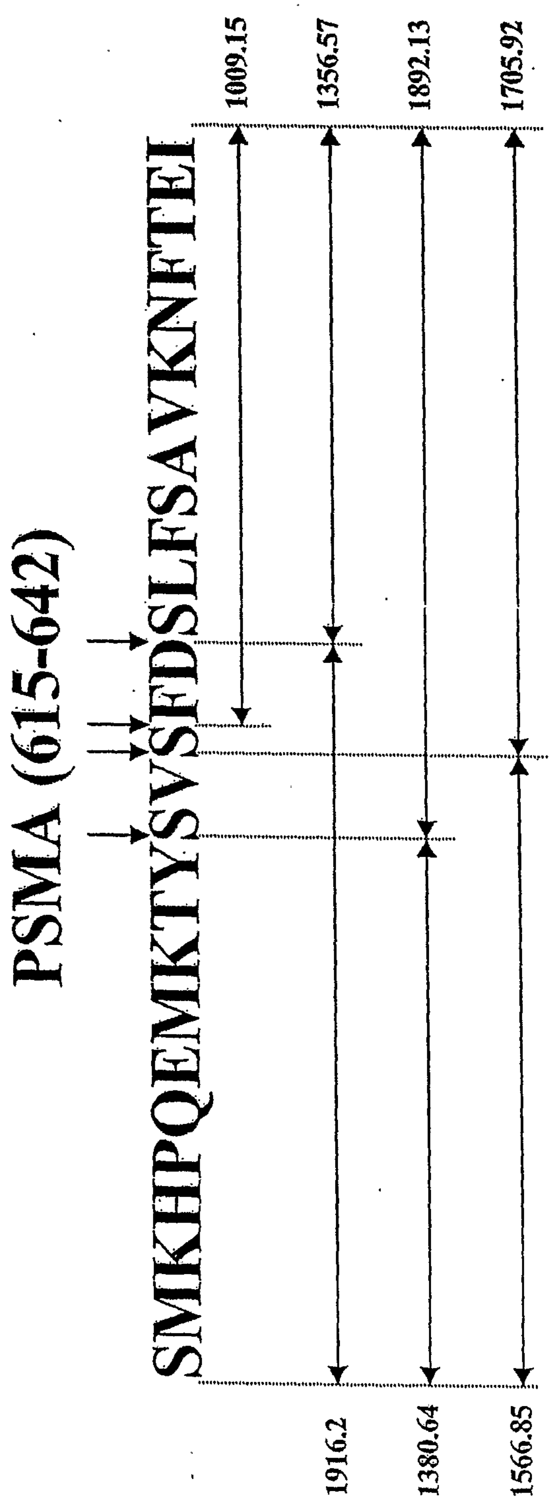

PSMA (597-623)
CRDYAVVLRKYADKIYSISMKHPQEMK
1115.53
1907.28
938.48
2177.59
2161.51
1977.35
1386.25
1814.17
1469.76
1370.63
1269.52

Figure 52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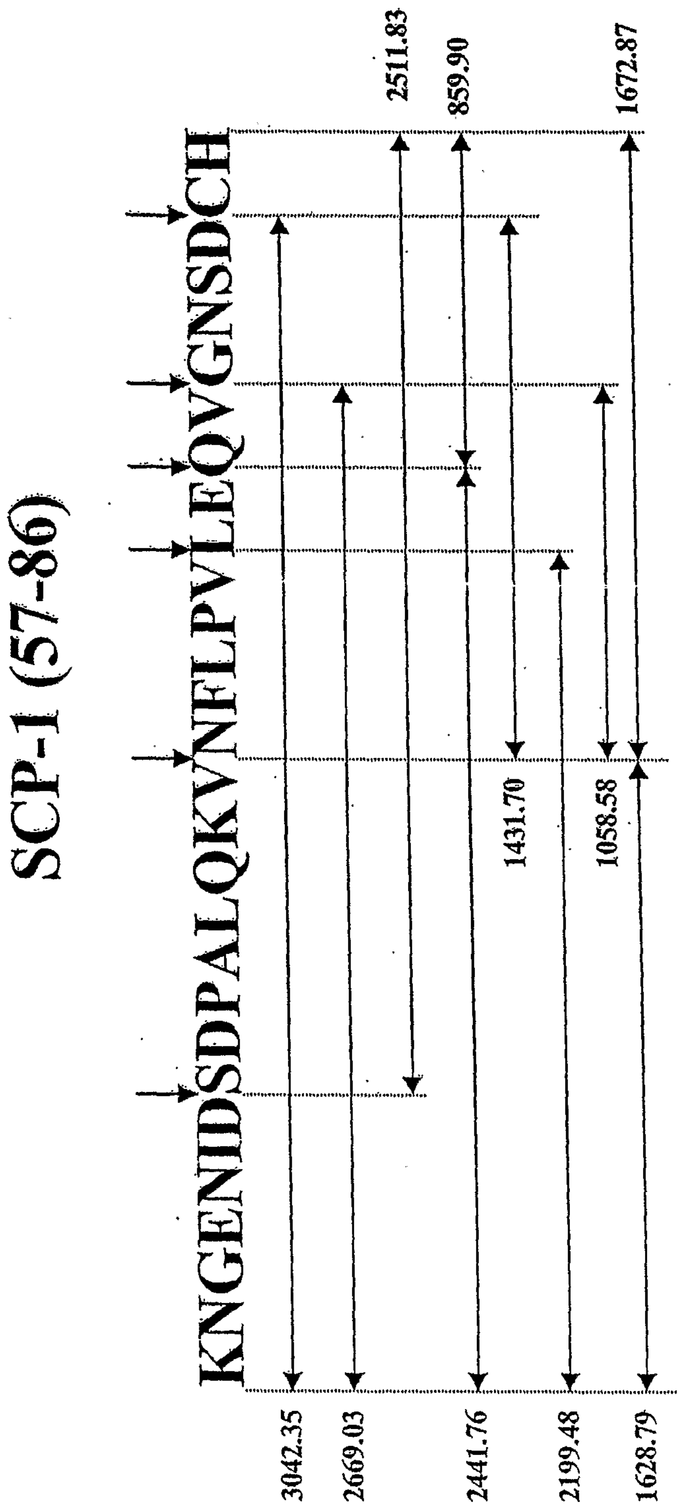
1566.85

Figure 53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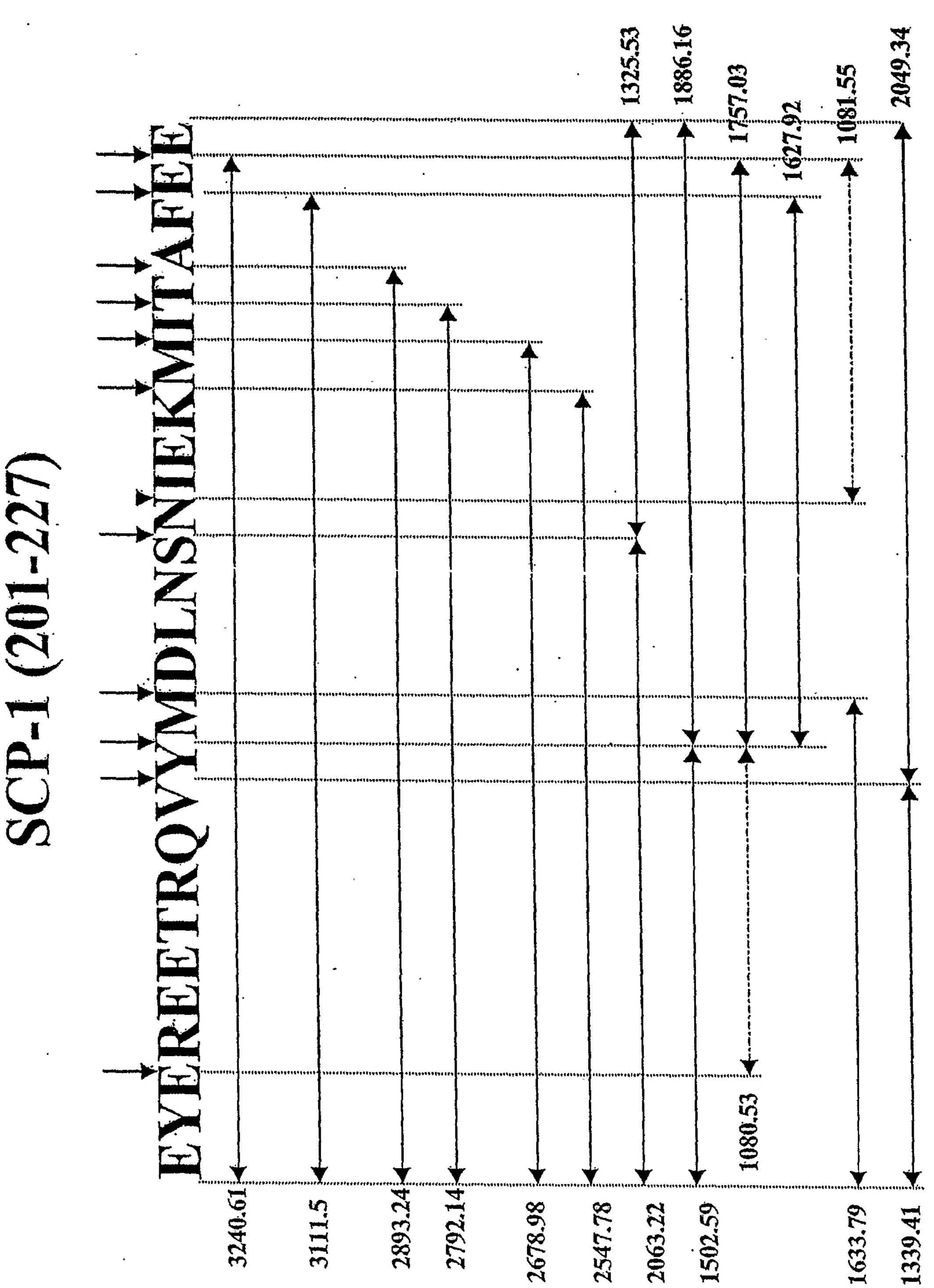
2441.76
2199.48
1628.79

Figure 54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2063.22
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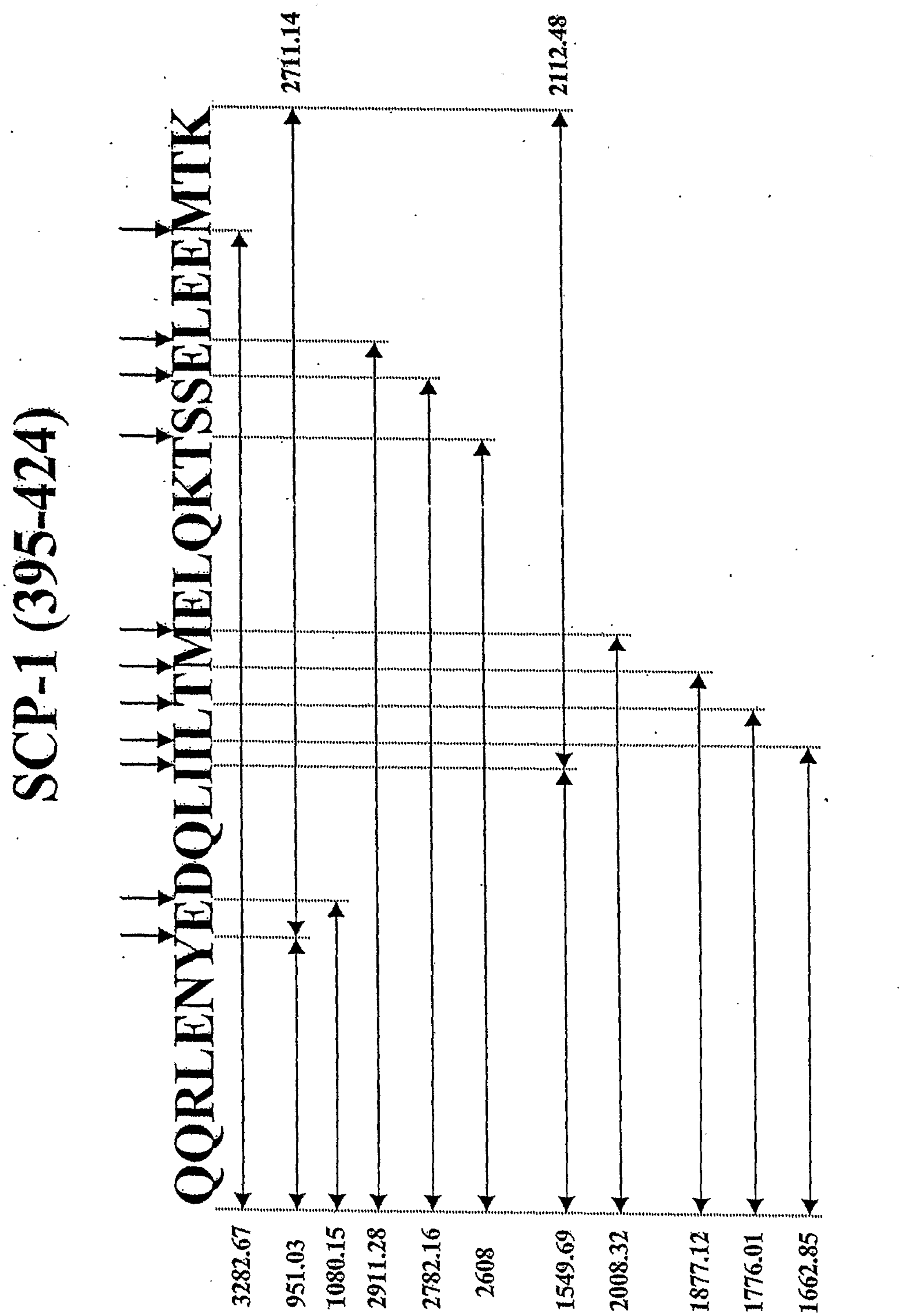
1627.92
1081.55
2049.34

Figure 55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2008.32
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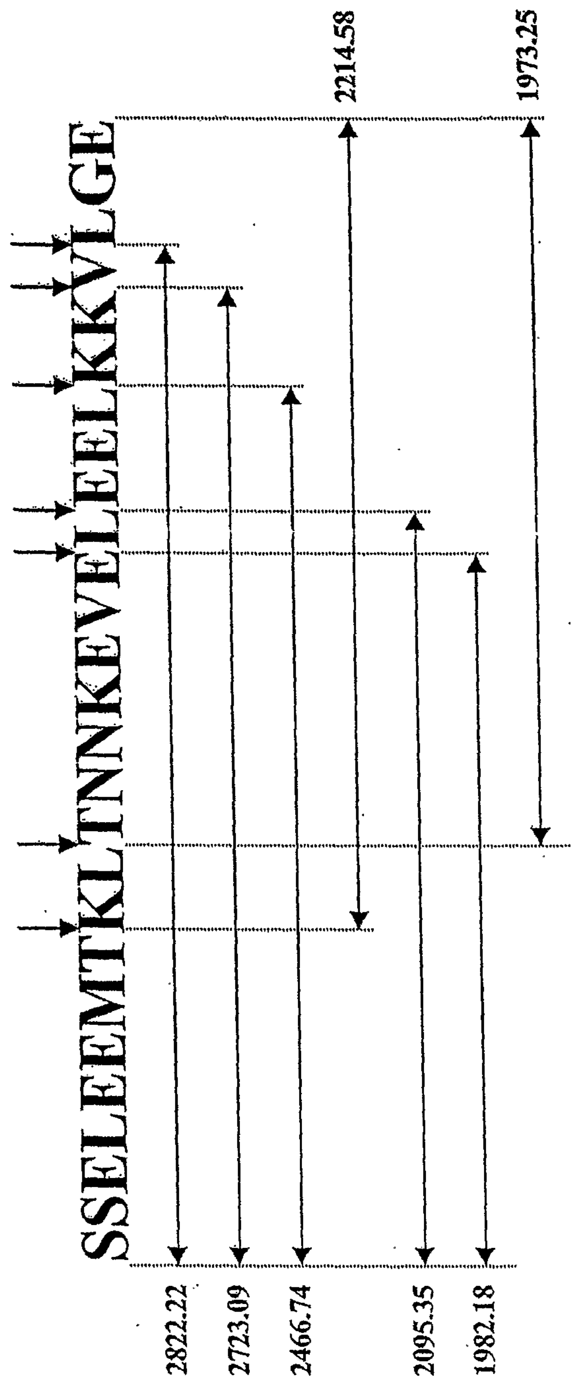
1776.01
1662.85

Figure 56

SCP-1 (416-442)



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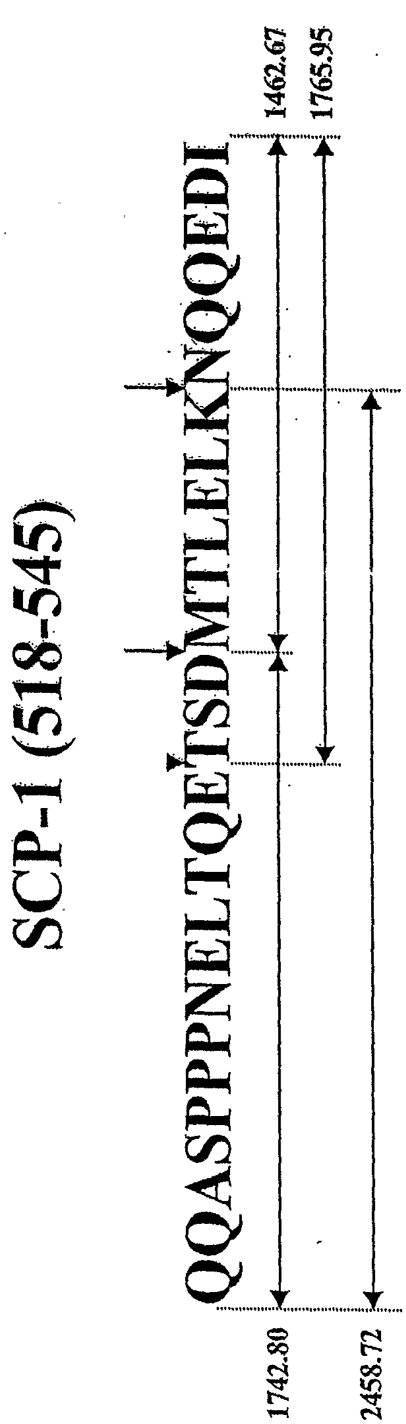
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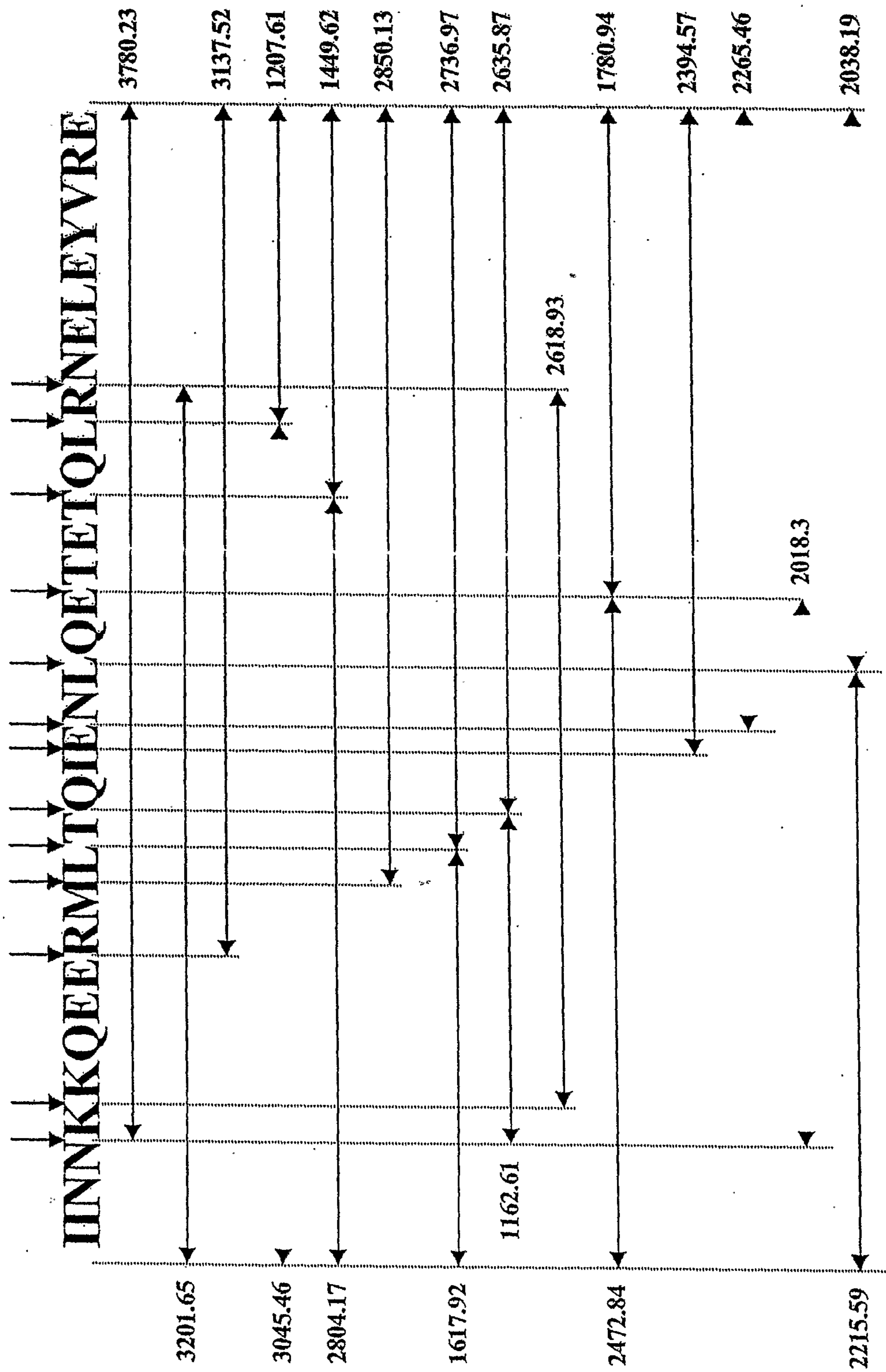
Figure 58

SCP-1 (545-578)



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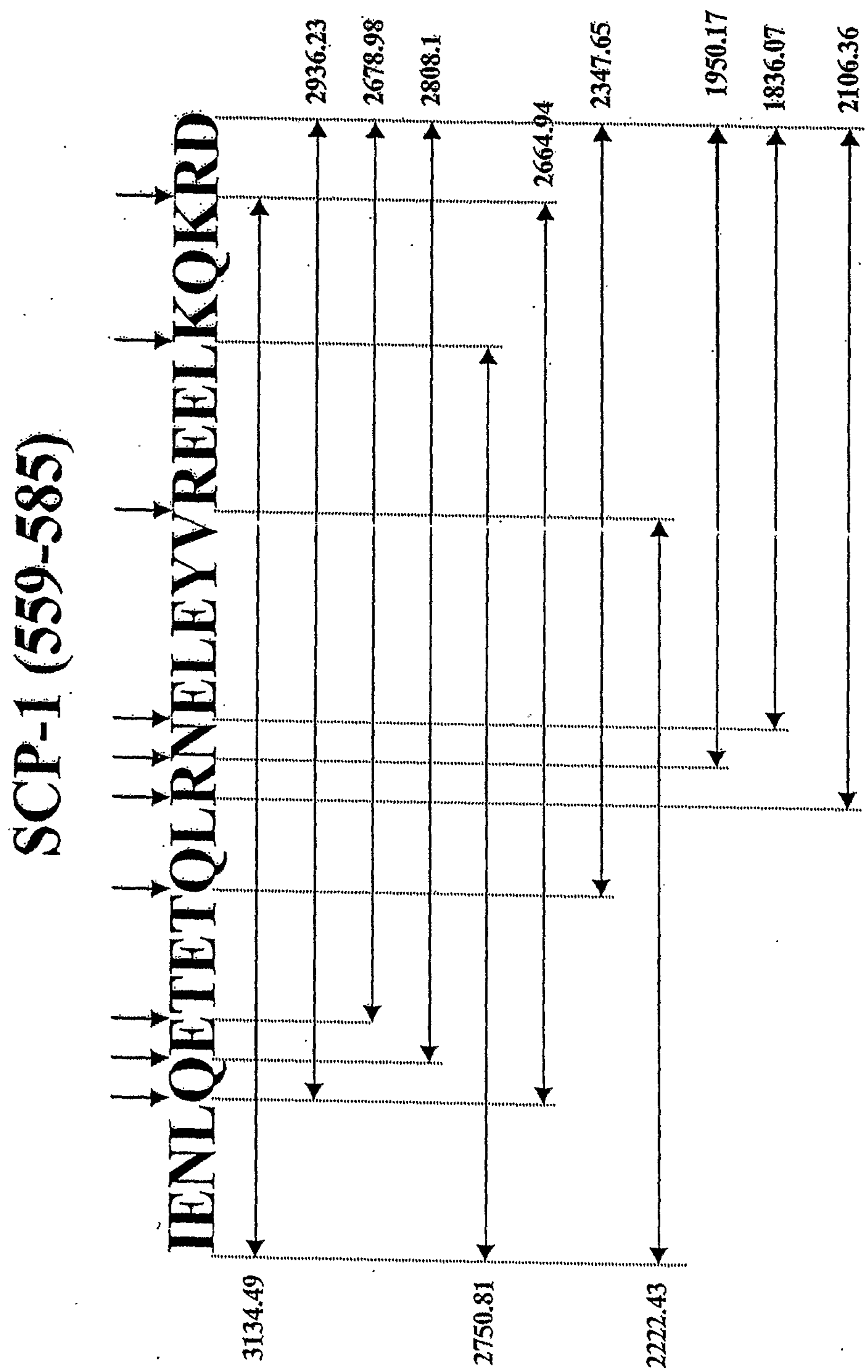
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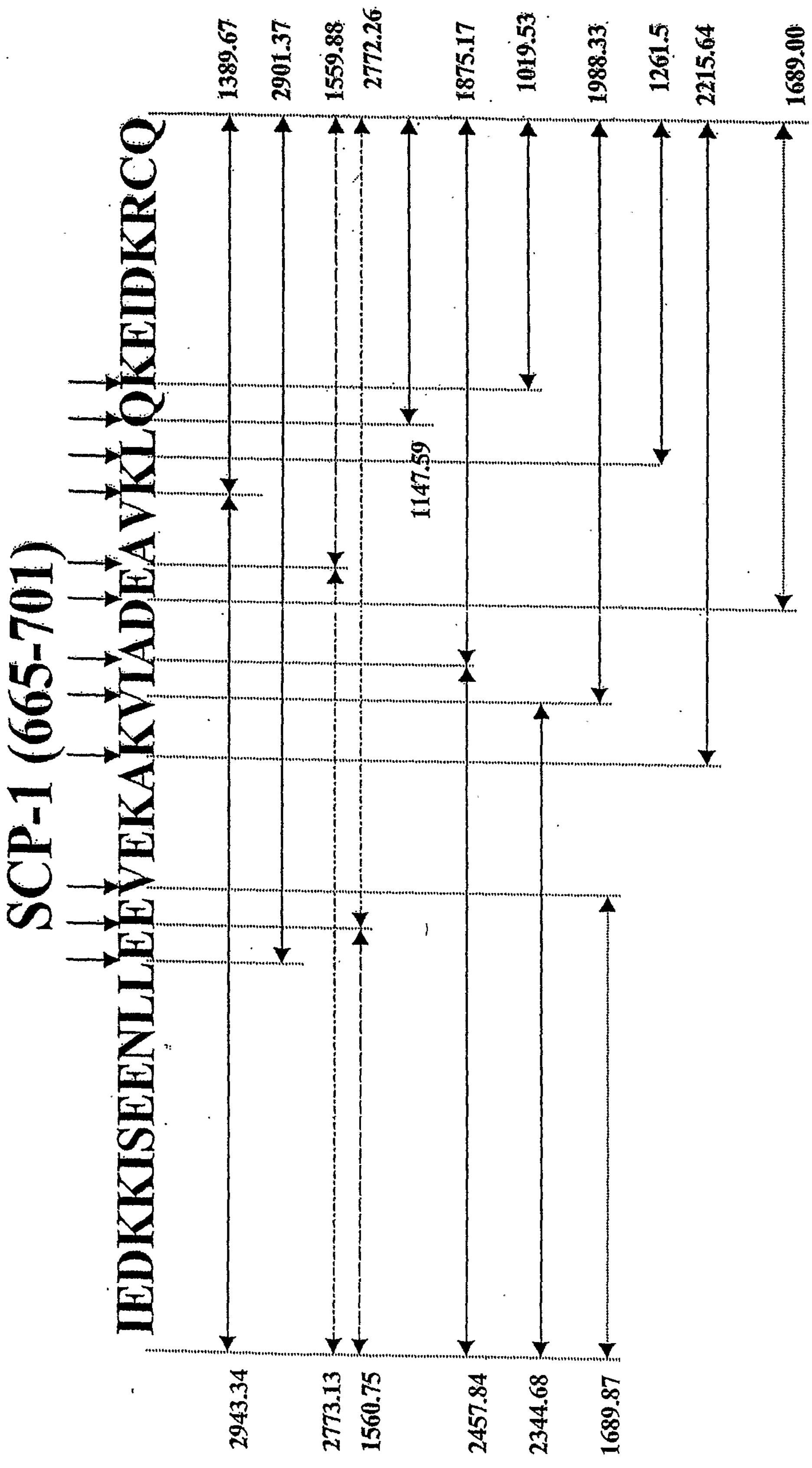
Figure 60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1988.33
1261.5
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Figure 61

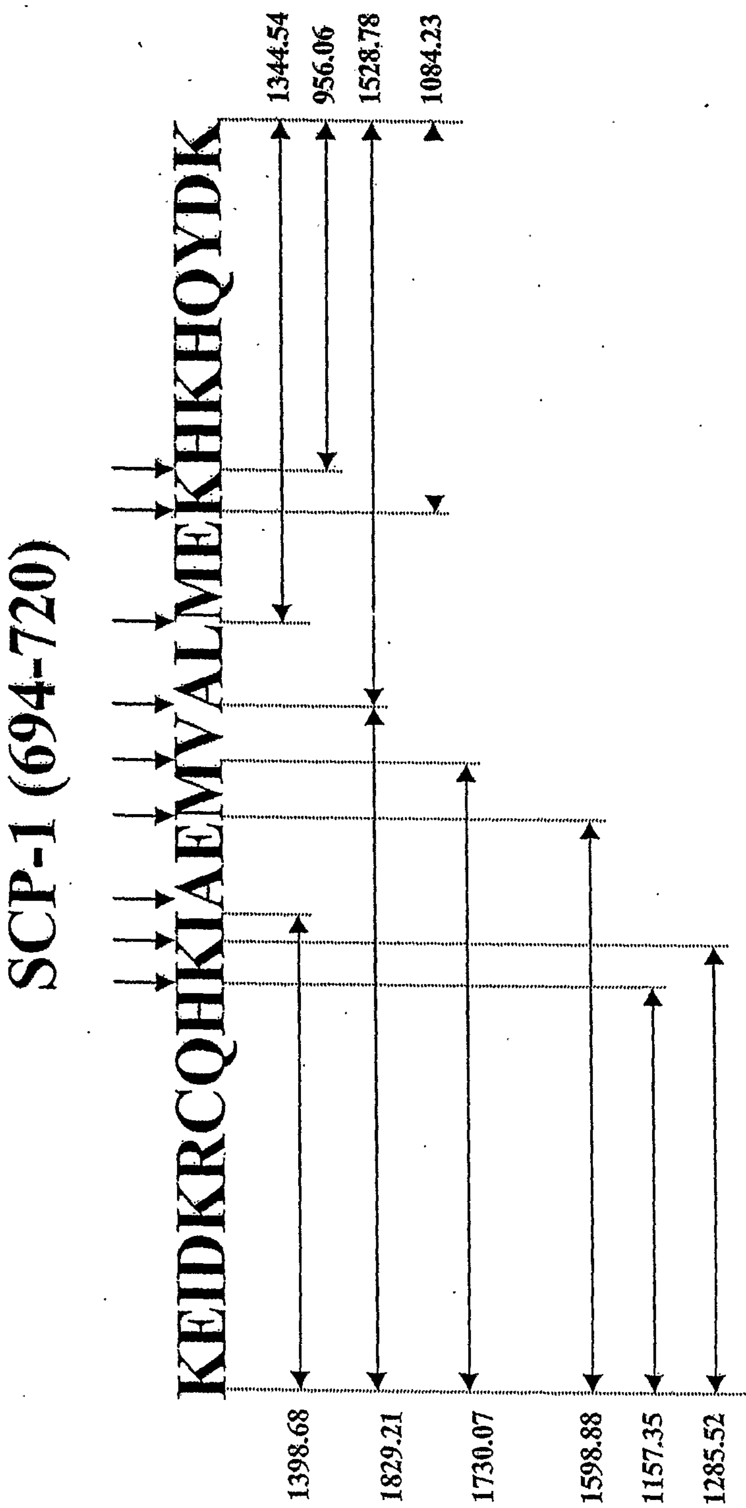
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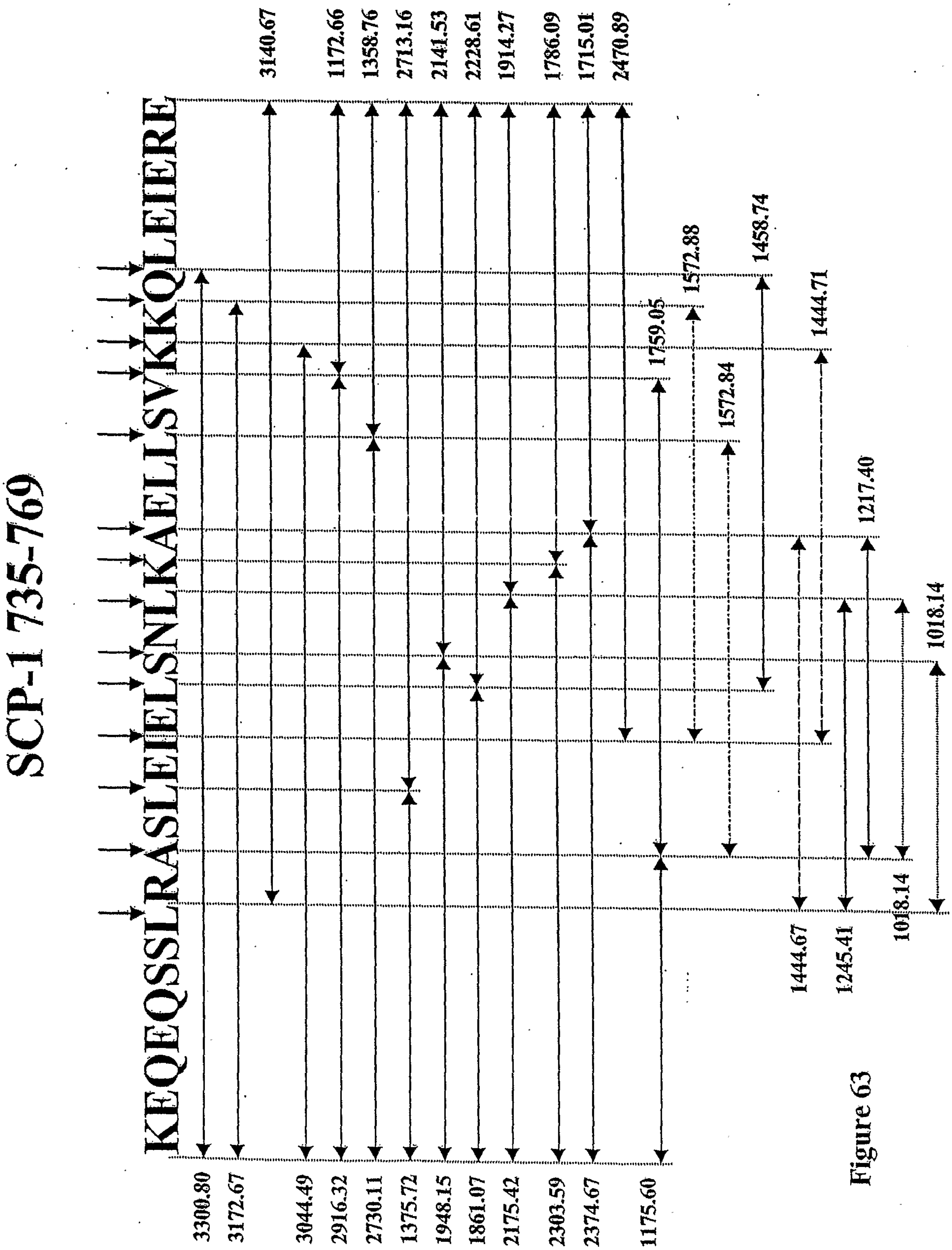
Figure 62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2228.61
1914.27
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2470.89
1759.05
1572.88
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1444.71
1217.40
1018.14
3300.80
3172.67
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2916.32
2730.11
1375.72
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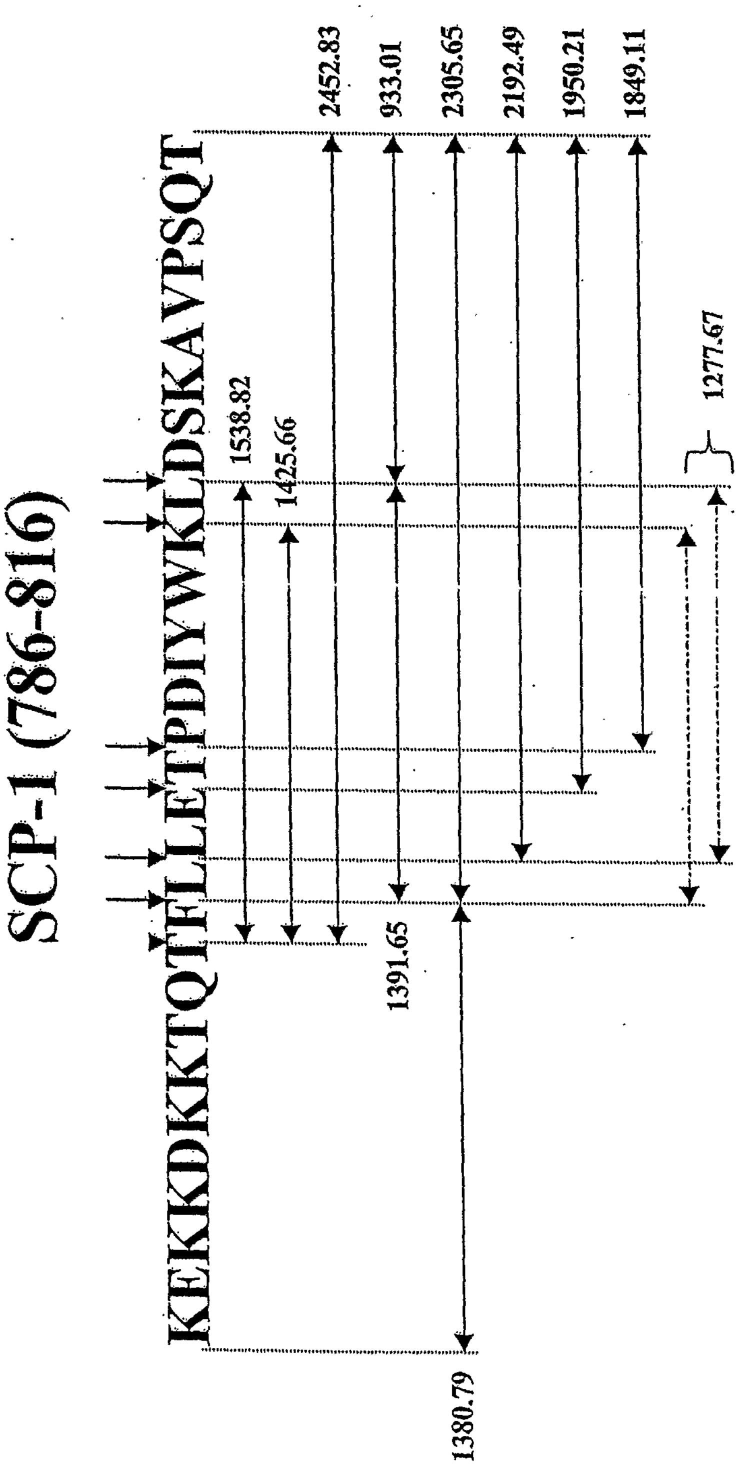
Figure 63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1380.79

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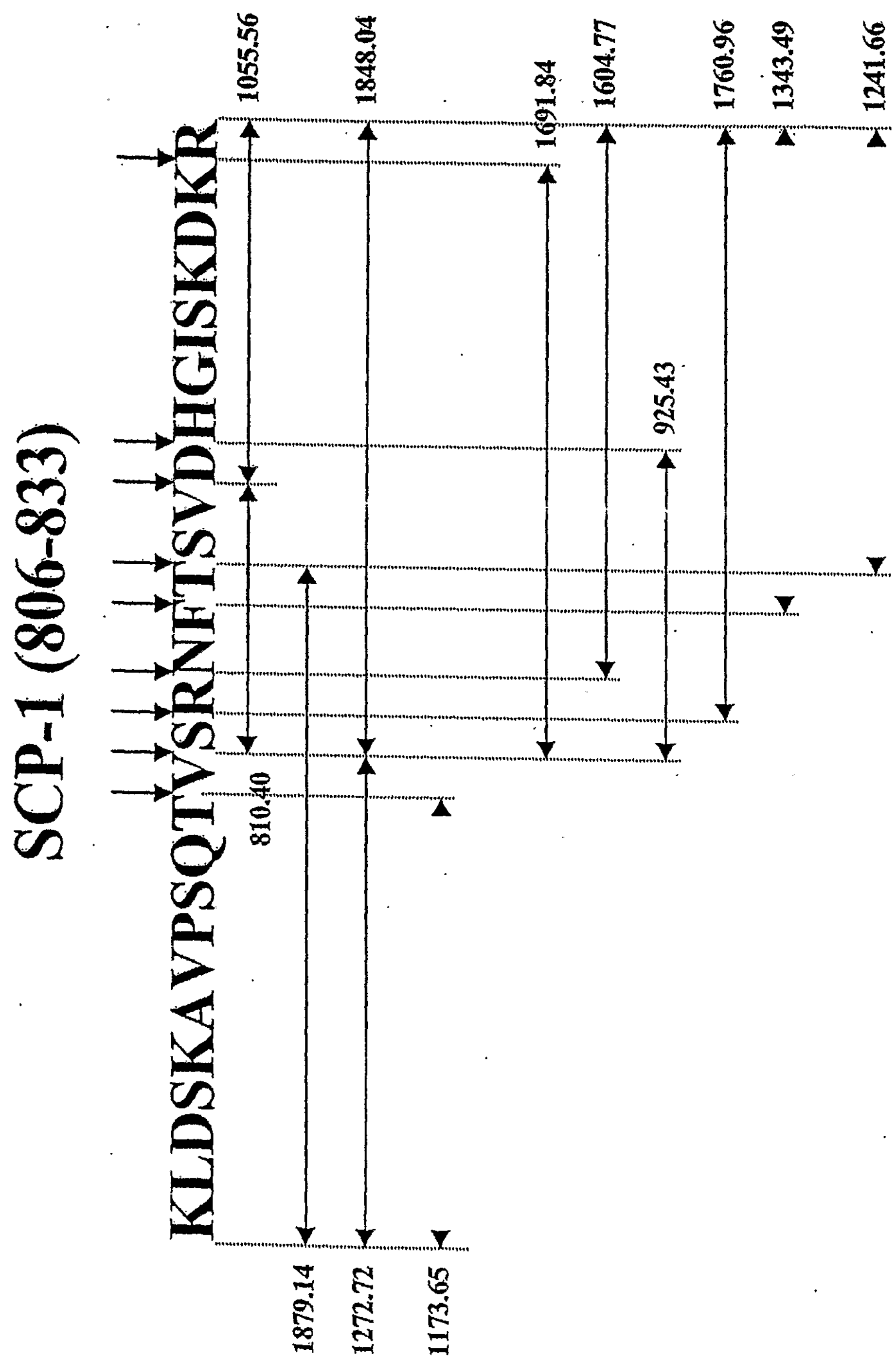
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Figure 65

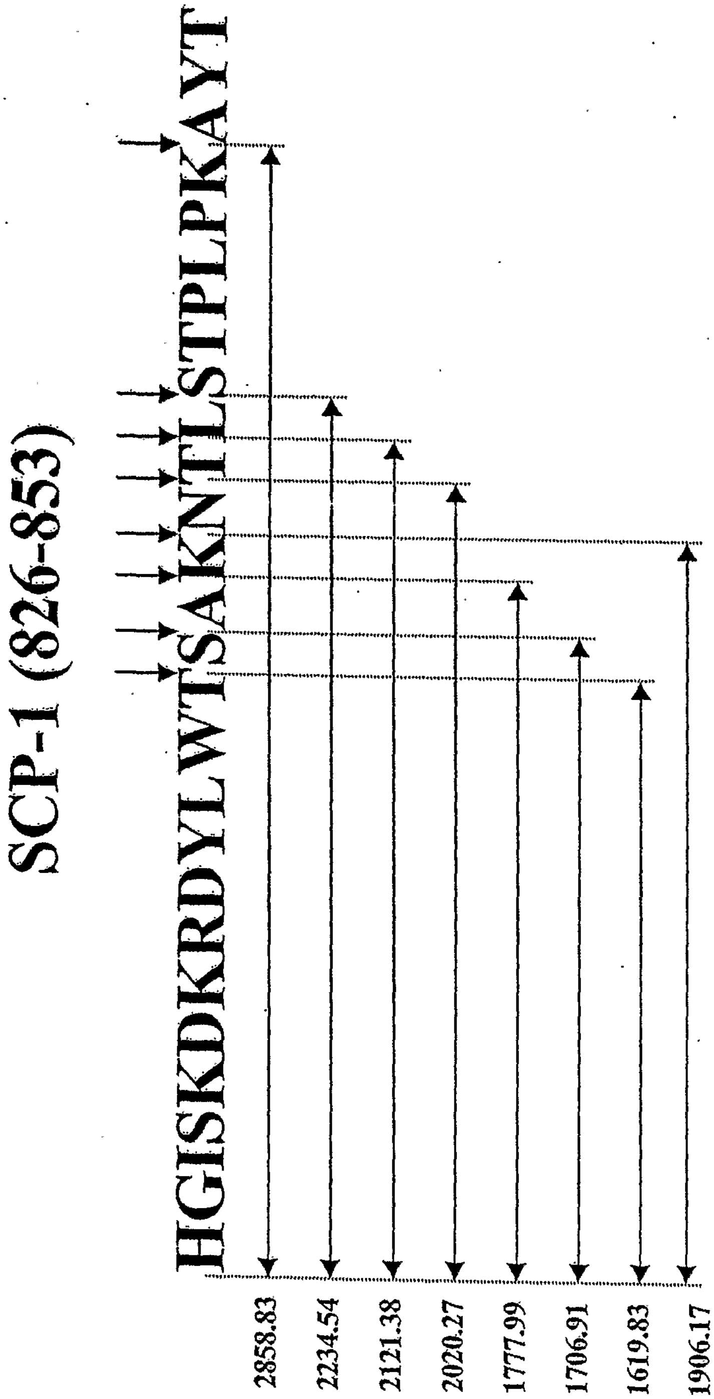
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Figure 66

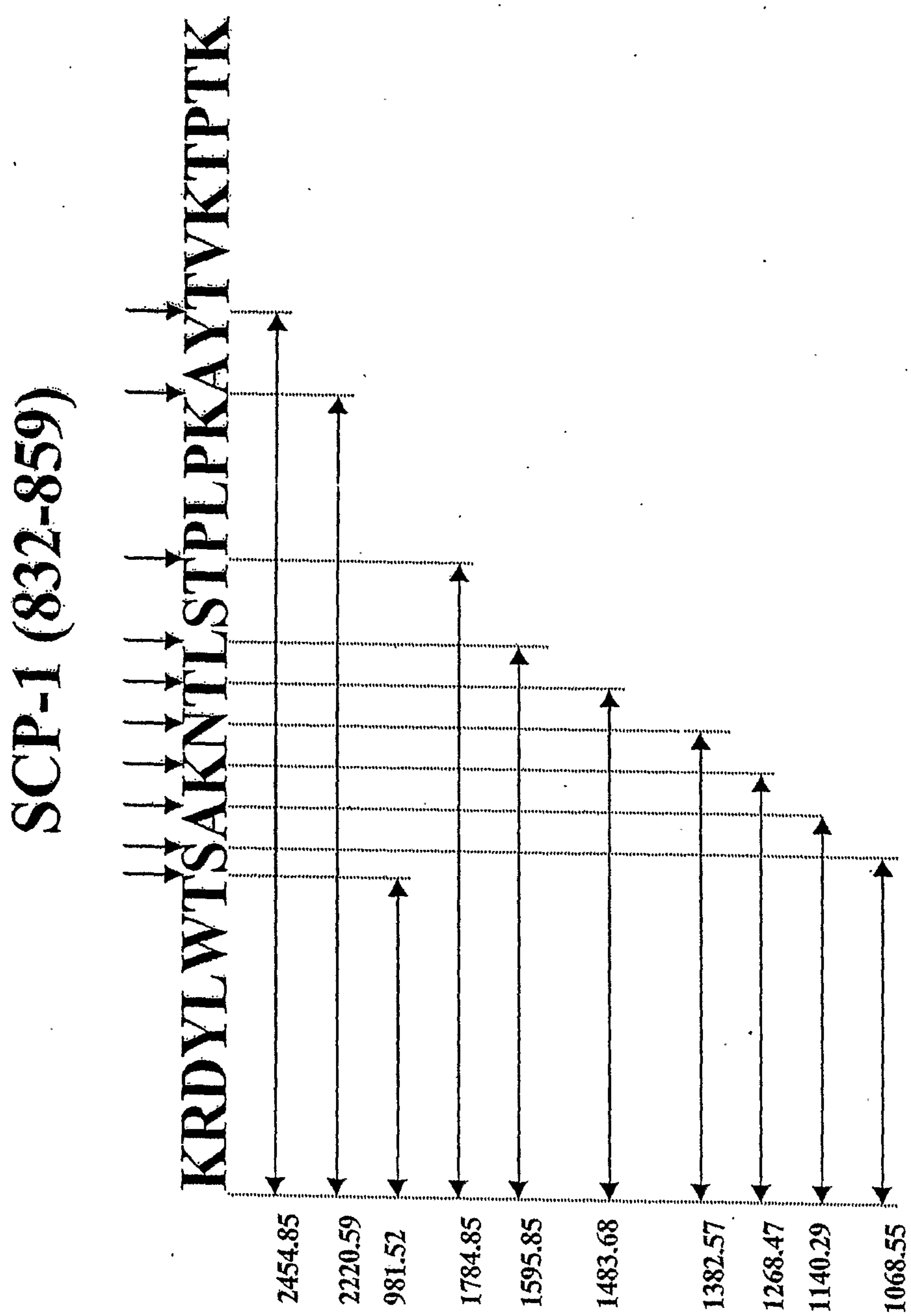
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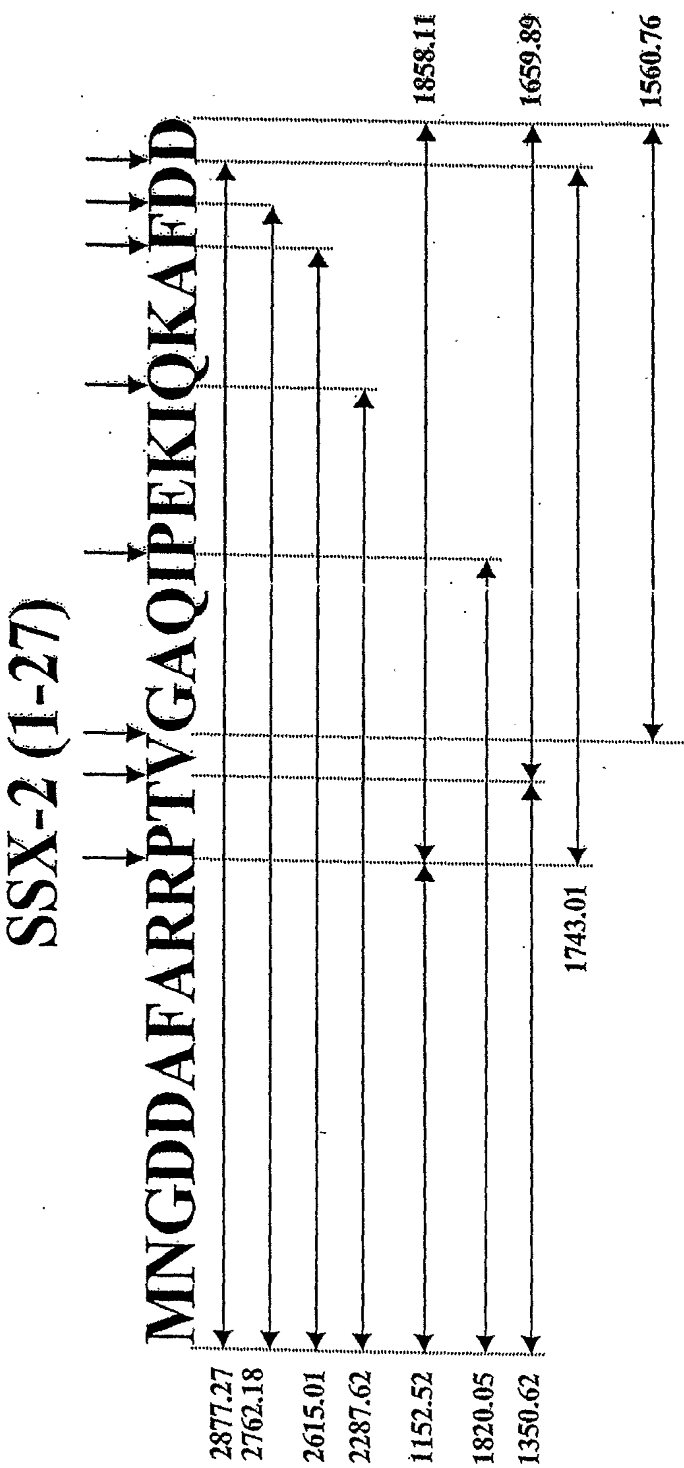
Figure 67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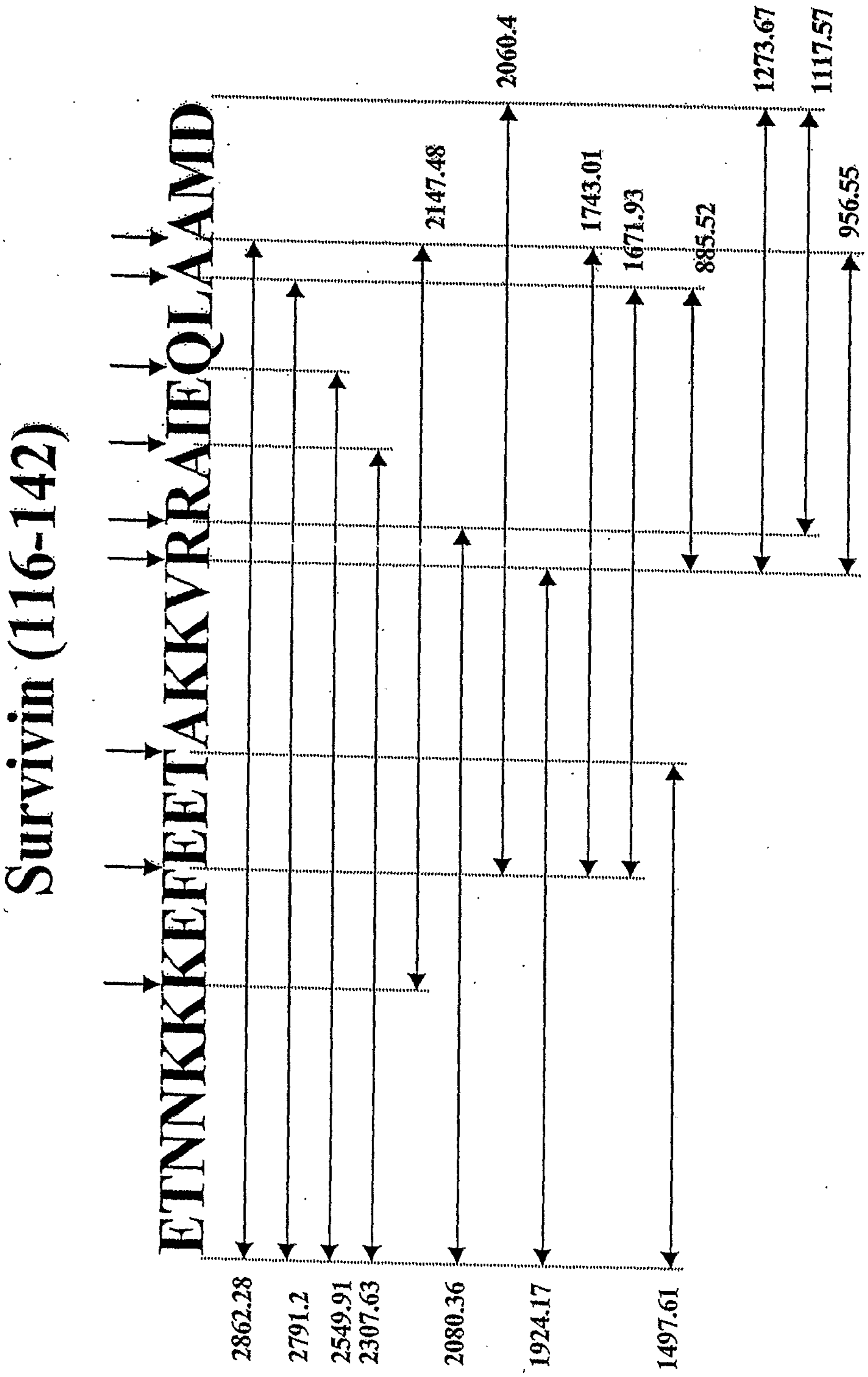
1560.76
1743.01

Figure 68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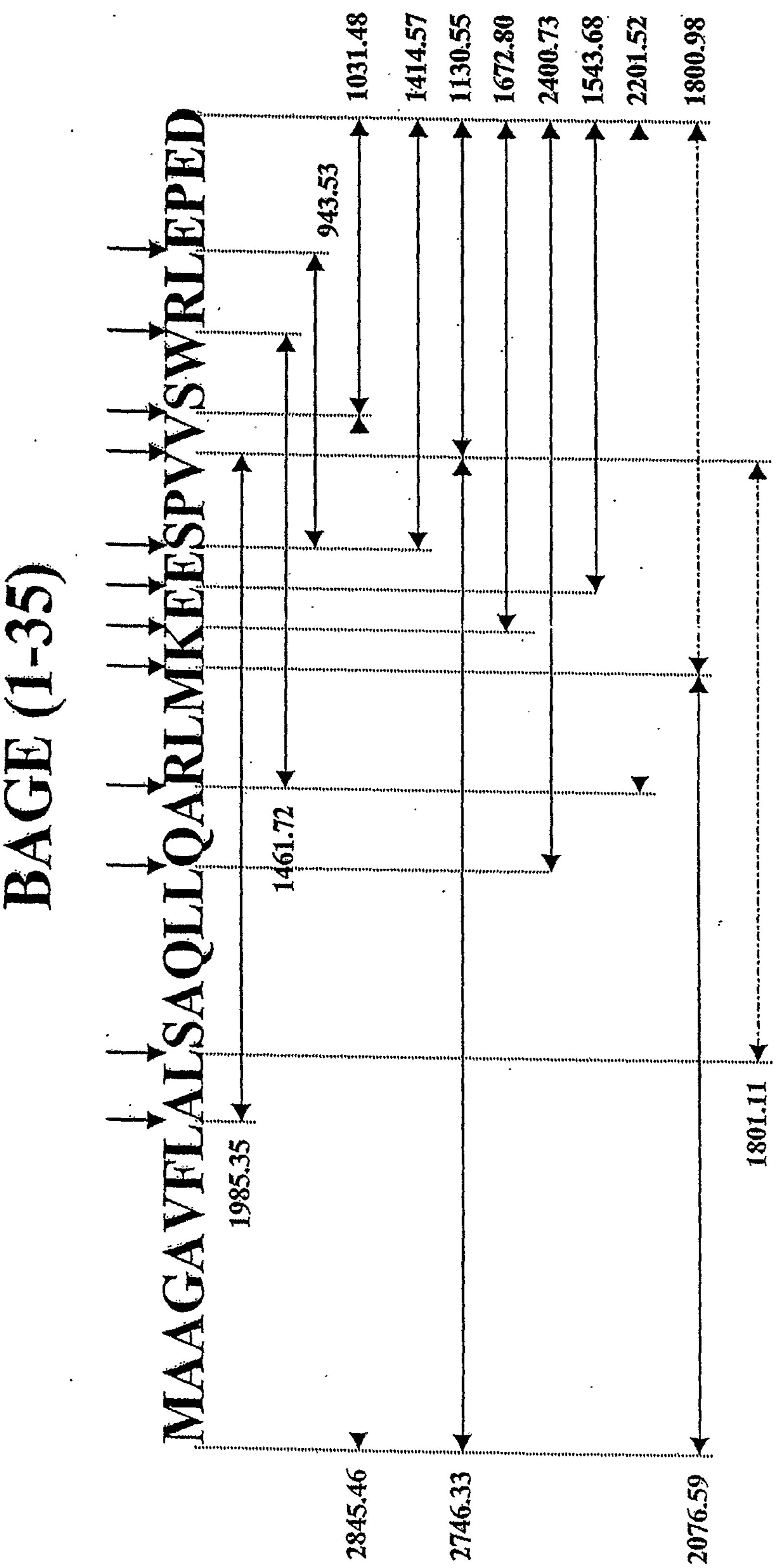
956.55

Figure 69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1543.68
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2746.33
2076.59

Figure 70

SEQUENCE LISTING

<110> MANNKIND CORPORATION
SIMARD, John J. L.
DIAMOND, David C.
LIU, Liping
LIU, Zheng

<120> EPITOPE SEQUENCES

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50 55 60
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Pro Glu Lys Asp Lys Phe Phe Ala Tyr Leu Thr Leu Ala Lys His Thr
130 135 140
Ile Ser Ser Asp Tyr Val Ile Pro Ile Gly Thr Tyr Gly Gln Met Lys
145 150 155 160
Asn Gly Ser Thr Pro Met Phe Asn Asp Ile Asn Ile Tyr Asp Leu Phe
165 170 175
Val Trp Met His Tyr Tyr Val Ser Met Asp Ala Leu Leu Gly Gly Ser
180 185 190

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Pro Trp His Arg Leu Phe Leu Leu Arg Trp Glu Gln Glu Ile Gln Lys
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225 230 235 240
Ala Glu Lys Cys Asp Ile Cys Thr Asp Glu Tyr Met Gly Gly Gln His
245 250 255
Pro Thr Asn Pro Asn Leu Leu Ser Pro Ala Ser Phe Phe Ser Ser Trp
260 265 270
Gln Ile Val Cys Ser Arg Leu Glu Glu Tyr Asn Ser His Gln Ser Leu
275 280 285
Cys Asn Gly Thr Pro Glu Gly Pro Leu Arg Arg Asn Pro Gly Asn His
290 295 300
Asp Lys Ser Arg Thr Pro Arg Leu Pro Ser Ser Ala Asp Val Glu Phe
305 310 315 320
Cys Leu Ser Leu Thr Gln Tyr Glu Ser Gly Ser Met Asp Lys Ala Ala
325 330 335
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340 345 350
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355 360 365
Tyr Met Asn Gly Thr Met Ser Gln Val Gln Gly Ser Ala Asn Asp Pro
370 375 380
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450 455 460
Lys Ser Tyr Leu Glu Gln Ala Ser Arg Ile Trp Ser Trp Leu Leu Gly
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485 490 495
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Ala Thr Leu Pro Pro Phe Met Cys Asn Lys Arg Ala Glu Asp Phe Gln

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Pro Gln Met Thr Phe Gly Arg Leu Gln Gly Ile Ser Pro Lys Ile Met
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Pro Lys Lys Pro Ala Glu Glu Gly Asn Asp Ser Glu Glu Val Pro Glu
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Gln Ser Gln Trp Lys Glu Phe Gly Leu Asp Ser Val Glu Leu Ala His
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Tyr Asp Val Leu Leu Ser Tyr Pro Asn Lys Thr His Pro Asn Tyr Ile
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Ser Ile Ile Asn Glu Asp Gly Asn Glu Ile Phe Asn Thr Ser Leu Phe
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Glu Pro Pro Pro Pro Gly Tyr Glu Asn Val Ser Asp Ile Val Pro Pro
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165 170 175
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Phe Arg Gly Asn Lys Val Lys Asn Ala Gln Leu Ala Gly Ala Lys Gly
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Val Ile Leu Tyr Ser Asp Pro Ala Asp Tyr Phe Ala Pro Gly Val Lys
225 230 235 240
Ser Tyr Pro Asp Gly Trp Asn Leu Pro Gly Gly Gly Val Gln Arg Gly
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Pro Ala Asn Glu Tyr Ala Tyr Arg Arg Gly Ile Ala Glu Ala Val Gly
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290 295 300

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Gly Ser Leu Lys Val Pro Tyr Asn Val Gly Pro Gly Phe Thr Gly Asn
325 330 335
Phe Ser Thr Gln Lys Val Lys Met His Ile His Ser Thr Asn Glu Val
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355 360 365
Asp Arg Tyr Val Ile Leu Gly Gly His Arg Asp Ser Trp Val Phe Gly
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Gly Ile Asp Pro Gln Ser Gly Ala Ala Val Val His Glu Ile Val Arg
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Glu Trp Ala Glu Glu Asn Ser Arg Leu Leu Gln Glu Arg Gly Val Ala
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485 490 495
Trp Thr Lys Lys Ser Pro Ser Pro Glu Phe Ser Gly Met Pro Arg Ile
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Ser Lys Leu Gly Ser Gly Asn Asp Phe Glu Val Phe Phe Gln Arg Leu
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545 550 555 560
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580 585 590
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Asp Lys Ile Tyr Ser Ile Ser Met Lys His Pro Gln Glu Met Lys Thr
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Glu Ile Ala Ser Lys Phe Ser Glu Arg Leu Gln Asp Phe Asp Lys Ser
645 650 655
Asn Pro Ile Val Leu Arg Met Met Asn Asp Gln Leu Met Phe Leu Glu
660 665 670
Arg Ala Phe Ile Asp Pro Leu Gly Leu Pro Asp Arg Pro Phe Tyr Arg
675 680 685
His Val Ile Tyr Ala Pro Ser Ser His Asn Lys Tyr Ala Gly Glu Ser
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Pro Glu Gly Asp Leu Val Tyr Val Asn Tyr
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1 5

<210> 41
<211> 10
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<400> 41
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1 5 10

<210> 42
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<400> 42
Asn Tyr Ala Arg Thr Glu Asp Phe Phe
1 5

<210> 43
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<400> 43
Tyr Ala Arg Thr Glu Asp Phe Phe
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Arg Thr Glu Asp Phe Phe Lys Leu Glu
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Tyr Tyr Asp Ala Gln Lys Leu Leu Glu
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Leu Pro Ser Ile Pro Val His Pro Ile
1 5

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<400> 48
Gly Leu Pro Ser Ile Pro Val His Pro Ile
1 5 10

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1 5

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Leu Arg Val Asp Cys Thr Pro Leu Met Tyr
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20 25 30
Pro Phe Tyr
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Ile Asp Pro Leu Gly Leu
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<210> 66
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Met Met Asn Asp Gln Leu Met Phe Leu
1 5

<210> 67
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Arg Met Met Asn Asp Gln Leu Met Phe Leu
1 5 10

<210> 68
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<213> Homo sapiens

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Arg Met Met Asn Asp Gln Leu Met Phe
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Tyr Pro Glu Trp Thr Glu Ala Gln Arg Leu Asp Cys Trp Arg Gly Gly
50 55 60
Gln Val Ser Leu Lys Val Ser Asn Asp Gly Pro Thr Leu Ile Gly Ala
65 70 75 80
Asn Ala Ser Phe Ser Ile Ala Leu Asn Phe Pro Gly Ser Gln Lys Val
85 90 95
Leu Pro Asp Gly Gln Val Ile Trp Val Asn Asn Thr Ile Ile Asn Gly
100 105 110
Ser Gln Val Trp Gly Gly Gln Pro Val Tyr Pro Gln Glu Thr Asp Asp
115 120 125
Ala Cys Ile Phe Pro Asp Gly Gly Pro Cys Pro Ser Gly Ser Trp Ser
130 135 140
Gln Lys Arg Ser Phe Val Tyr Val Trp Lys Thr Trp Gly Gln Tyr Trp
145 150 155 160
Gln Val Leu Gly Gly Pro Val Ser Gly Leu Ser Ile Gly Thr Gly Arg
165 170 175
Ala Met Leu Gly Thr His Thr Met Glu Val Thr Val Tyr His Arg Arg
180 185 190
Gly Ser Arg Ser Tyr Val Pro Leu Ala His Ser Ser Ser Ala Phe Thr
195 200 205
Ile Thr Asp Gln Val Pro Phe Ser Val Ser Val Ser Gln Leu Arg Ala
210 215 220
Leu Asp Gly Gly Asn Lys His Phe Leu Arg Asn Gln Pro Leu Thr Phe
225 230 235 240
Ala Leu Gln Leu His Asp Pro Ser Gly Tyr Leu Ala Glu Ala Asp Leu
245 250 255
Ser Tyr Thr Trp Asp Phe Gly Asp Ser Ser Gly Thr Leu Ile Ser Arg
260 265 270
Ala Pro Val Val Thr His Thr Tyr Leu Glu Pro Gly Pro Val Thr Ala
275 280 285

Gln Val Val Leu Gln Ala Ala Ile Pro Leu Thr Ser Cys Gly Ser Ser
290 295 300
Pro Val Pro Gly Thr Thr Asp Gly His Arg Pro Thr Ala Glu Ala Pro
305 310 315 320
Asn Thr Thr Ala Gly Gln Val Pro Thr Thr Glu Val Val Gly Thr Thr
325 330 335
Pro Gly Gln Ala Pro Thr Ala Glu Pro Ser Gly Thr Thr Ser Val Gln
340 345 350
Val Pro Thr Thr Glu Val Ile Ser Thr Ala Pro Val Gln Met Pro Thr
355 360 365
Ala Glu Ser Thr Gly Met Thr Pro Glu Lys Val Pro Val Ser Glu Val
370 375 380
Met Gly Thr Thr Leu Ala Glu Met Ser Thr Pro Glu Ala Thr Gly Met
385 390 395 400
Thr Pro Ala Glu Val Ser Ile Val Val Leu Ser Gly Thr Thr Ala Ala
405 410 415
Gln Val Thr Thr Thr Glu Trp Val Glu Thr Thr Ala Arg Glu Leu Pro
420 425 430
Ile Pro Glu Pro Glu Gly Pro Asp Ala Ser Ser Ile Met Ser Thr Glu
435 440 445
Ser Ile Thr Gly Ser Leu Gly Pro Leu Leu Asp Gly Thr Ala Thr Leu
450 455 460
Arg Leu Val Lys Arg Gln Val Pro Leu Asp Cys Val Leu Tyr Arg Tyr
465 470 475 480
Gly Ser Phe Ser Val Thr Leu Asp Ile Val Gln Gly Ile Glu Ser Ala
485 490 495
Glu Ile Leu Gln Ala Val Pro Ser Gly Glu Gly Asp Ala Phe Glu Leu
500 505 510
Thr Val Ser Cys Gln Gly Gly Leu Pro Lys Glu Ala Cys Met Glu Ile
515 520 525
Ser Ser Pro Gly Cys Gln Pro Pro Ala Gln Arg Leu Cys Gln Pro Val
530 535 540
Leu Pro Ser Pro Ala Cys Gln Leu Val Leu His Gln Ile Leu Lys Gly
545 550 555 560
Gly Ser Gly Thr Tyr Cys Leu Asn Val Ser Leu Ala Asp Thr Asn Ser
565 570 575
Leu Ala Val Val Ser Thr Gln Leu Ile Met Pro Gly Gln Glu Ala Gly
580 585 590
Leu Gly Gln Val Pro Leu Ile Val Gly Ile Leu Leu Val Leu Met Ala
595 600 605
Val Val Leu Ala Ser Leu Ile Tyr Arg Arg Arg Leu Met Lys Gln Asp
610 615 620
Phe Ser Val Pro Gln Leu Pro His Ser Ser Ser His Trp Leu Arg Leu
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Ser Gly Gln Gln Val
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20 25 30
Ser Ser Ser Ser Pro Leu Val Leu Gly Thr Leu Glu Glu Val Pro Thr

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Pro Thr Thr Ile Asn Phe Thr Arg Gln Arg Gln Pro Ser Glu Gly Ser
65                  70                  75                  80
Ser Ser Arg Glu Glu Glu Gly Pro Ser Thr Ser Cys Ile Leu Glu Ser
                85                  90                  95
Leu Phe Arg Ala Val Ile Thr Lys Lys Val Ala Asp Leu Val Gly Phe
            100                 105                 110
Leu Leu Leu Lys Tyr Arg Ala Arg Glu Pro Val Thr Lys Ala Glu Met
        115                 120                 125
Leu Glu Ser Val Ile Lys Asn Tyr Lys His Cys Phe Pro Glu Ile Phe
    130                 135                 140
Gly Lys Ala Ser Glu Ser Leu Gln Leu Val Phe Gly Ile Asp Val Lys
145                 150                 155                 160
Glu Ala Asp Pro Thr Gly His Ser Tyr Val Leu Val Thr Cys Leu Gly
                165                 170                 175
Leu Ser Tyr Asp Gly Leu Leu Gly Asp Asn Gln Ile Met Pro Lys Thr
            180                 185                 190
Gly Phe Leu Ile Ile Val Leu Val Met Ile Ala Met Glu Gly Gly His
        195                 200                 205
Ala Pro Glu Glu Glu Ile Trp Glu Glu Leu Ser Val Met Glu Val Tyr
    210                 215                 220
Asp Gly Arg Glu His Ser Ala Tyr Gly Glu Pro Arg Lys Leu Leu Thr
225                 230                 235                 240
Gln Asp Leu Val Gln Glu Lys Tyr Leu Glu Tyr Arg Gln Val Pro Asp
                245                 250                 255
Ser Asp Pro Ala Arg Tyr Glu Phe Leu Trp Gly Pro Arg Ala Leu Ala
            260                 265                 270
Glu Thr Ser Tyr Val Lys Val Leu Glu Tyr Val Ile Lys Val Ser Ala
        275                 280                 285
Arg Val Arg Phe Phe Phe Pro Ser Leu Arg Glu Ala Ala Leu Arg Glu
    290                 295                 300
Glu Glu Glu Gly Val
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<213> Homo sapiens

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            20                  25                  30
Thr Glu Glu Gln Gln Thr Ala Ser Ser Ser Ser Thr Leu Val Glu Val
        35                  40                  45
Thr Leu Gly Glu Val Pro Ala Ala Asp Ser Pro Ser Pro Pro His Ser
    50                  55                  60
Pro Gln Gly Ala Ser Ser Phe Ser Thr Thr Ile Asn Tyr Thr Leu Trp
65                  70                  75                  80
Arg Gln Ser Asp Glu Gly Ser Ser Asn Gln Glu Glu Glu Gly Pro Arg
                85                  90                  95
Met Phe Pro Asp Leu Glu Ser Glu Phe Gln Ala Ala Ile Ser Arg Lys
            100                 105                 110
Met Val Glu Leu Val His Phe Leu Leu Leu Lys Tyr Arg Ala Arg Glu
        115                 120                 125
Pro Val Thr Lys Ala Glu Met Leu Glu Ser Val Leu Arg Asn Cys Gln
    130                 135                 140
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Asp Phe Phe Pro Val Ile Phe Ser Lys Ala Ser Glu Tyr Leu Gln Leu
145 150 155 160
Val Phe Gly Ile Glu Val Val Glu Val Val Pro Ile Ser His Leu Tyr
165 170 175
Ile Leu Val Thr Cys Leu Gly Leu Ser Tyr Asp Gly Leu Leu Gly Asp
180 185 190
Asn Gln Val Met Pro Lys Thr Gly Leu Leu Ile Ile Val Leu Ala Ile
195 200 205
Ile Ala Ile Glu Gly Asp Cys Ala Pro Glu Glu Lys Ile Trp Glu Glu
210 215 220
Leu Ser Met Leu Glu Val Phe Glu Gly Arg Glu Asp Ser Val Phe Ala
225 230 235 240
His Pro Arg Lys Leu Leu Met Gln Asp Leu Val Gln Glu Asn Tyr Leu
245 250 255
Glu Tyr Arg Gln Val Pro Gly Ser Asp Pro Ala Cys Tyr Glu Phe Leu
260 265 270
Trp Gly Pro Arg Ala Leu Ile Glu Thr Ser Tyr Val Lys Val Leu His
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His Glu Arg Ala Leu Arg Glu Gly Glu Glu
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35 40 45
Thr Leu Gly Glu Val Pro Ala Ala Glu Ser Pro Asp Pro Pro Gln Ser
50 55 60
Pro Gln Gly Ala Ser Ser Leu Pro Thr Thr Met Asn Tyr Pro Leu Trp
65 70 75 80
Ser Gln Ser Tyr Glu Asp Ser Ser Asn Gln Glu Glu Glu Gly Pro Ser
85 90 95
Thr Phe Pro Asp Leu Glu Ser Glu Phe Gln Ala Ala Leu Ser Arg Lys
100 105 110
Val Ala Glu Leu Val His Phe Leu Leu Leu Lys Tyr Arg Ala Arg Glu
115 120 125
Pro Val Thr Lys Ala Glu Met Leu Gly Ser Val Val Gly Asn Trp Gln
130 135 140
Tyr Phe Phe Pro Val Ile Phe Ser Lys Ala Ser Ser Ser Leu Gln Leu
145 150 155 160
Val Phe Gly Ile Glu Leu Met Glu Val Asp Pro Ile Gly His Leu Tyr
165 170 175
Ile Phe Ala Thr Cys Leu Gly Leu Ser Tyr Asp Gly Leu Leu Gly Asp
180 185 190
Asn Gln Ile Met Pro Lys Ala Gly Leu Leu Ile Ile Val Leu Ala Ile
195 200 205
Ile Ala Arg Glu Gly Asp Cys Ala Pro Glu Glu Lys Ile Trp Glu Glu
210 215 220
Leu Ser Val Leu Glu Val Phe Glu Gly Arg Glu Asp Ser Ile Leu Gly
225 230 235 240
Asp Pro Lys Lys Leu Leu Thr Gln His Phe Val Gln Glu Asn Tyr Leu

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                245                     250                     255
Glu Tyr Arg Gln Val Pro Gly Ser Asp Pro Ala Cys Tyr Glu Phe Leu
            260                     265                     270
Trp Gly Pro Arg Ala Leu Val Glu Thr Ser Tyr Val Lys Val Leu His
        275                     280                     285
His Met Val Lys Ile Ser Gly Gly Pro His Ile Ser Tyr Pro Pro Leu
    290                     295                     300
His Glu Trp Val Leu Arg Glu Gly Glu Glu
305                     310


<210> 74
<211> 180
<212> PRT
<213> Homo sapiens

<400> 74
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 1               5                  10                  15
Gly Pro Gly Gly Pro Gly Ile Pro Asp Gly Pro Gly Gly Asn Ala Gly
            20                  25                  30
Gly Pro Gly Glu Ala Gly Ala Thr Gly Gly Arg Gly Pro Arg Gly Ala
        35                  40                  45
Gly Ala Ala Arg Ala Ser Gly Pro Gly Gly Gly Ala Pro Arg Gly Pro
    50                  55                  60
His Gly Gly Ala Ala Ser Gly Leu Asn Gly Cys Cys Arg Cys Gly Ala
65                  70                  75                  80
Arg Gly Pro Glu Ser Arg Leu Leu Glu Phe Tyr Leu Ala Met Pro Phe
                85                  90                  95
Ala Thr Pro Met Glu Ala Glu Leu Ala Arg Arg Ser Leu Ala Gln Asp
            100                 105                 110
Ala Pro Pro Leu Pro Val Pro Gly Val Leu Leu Lys Glu Phe Thr Val
        115                 120                 125
Ser Gly Asn Ile Leu Thr Ile Arg Leu Thr Ala Ala Asp His Arg Gln
    130                 135                 140
Leu Gln Leu Ser Ile Ser Ser Cys Leu Gln Gln Leu Ser Leu Leu Met
145                 150                 155                 160
Trp Ile Thr Gln Cys Phe Leu Pro Val Phe Leu Ala Gln Pro Pro Ser
                165                 170                 175
Gly Gln Arg Arg
            180


<210> 75
<211> 180
<212> PRT
<213> Homo sapiens

<400> 75
Met Gln Ala Glu Gly Arg Gly Thr Gly Gly Ser Thr Gly Asp Ala Asp
 1               5                  10                  15
Gly Pro Gly Gly Pro Gly Ile Pro Asp Gly Pro Gly Gly Asn Ala Gly
            20                  25                  30
Gly Pro Gly Glu Ala Gly Ala Thr Gly Gly Arg Gly Pro Arg Gly Ala
        35                  40                  45
Gly Ala Ala Arg Ala Ser Gly Pro Arg Gly Gly Ala Pro Arg Gly Pro
    50                  55                  60
His Gly Gly Ala Ala Ser Ala Gln Asp Gly Arg Cys Pro Cys Gly Ala
65                  70                  75                  80
Arg Arg Pro Asp Ser Arg Leu Leu Glu Leu His Ile Thr Met Pro Phe
                85                  90                  95
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Ser Ser Pro Met Glu Ala Glu Leu Val Arg Arg Ile Leu Ser Arg Asp
            100                 105                 110
Ala Ala Pro Leu Pro Arg Pro Gly Ala Val Leu Lys Asp Phe Thr Val
        115                 120                 125
Ser Gly Asn Leu Leu Phe Ile Arg Leu Thr Ala Ala Asp His Arg Gln
    130                 135                 140
Leu Gln Leu Ser Ile Ser Ser Cys Leu Gln Gln Leu Ser Leu Leu Met
145                 150                 155                 160
Trp Ile Thr Gln Cys Phe Leu Pro Val Phe Leu Ala Gln Ala Pro Ser
                165                 170                 175
Gly Gln Arg Arg
            180


<210> 76
<211> 210
<212> PRT
<213> Homo sapiens

<400> 76
Met Gln Ala Glu Gly Arg Gly Thr Gly Gly Ser Thr Gly Asp Ala Asp
 1               5                  10                  15
Gly Pro Gly Gly Pro Gly Ile Pro Asp Gly Pro Gly Gly Asn Ala Gly
            20                  25                  30
Gly Pro Gly Glu Ala Gly Ala Thr Gly Gly Arg Gly Pro Arg Gly Ala
        35                  40                  45
Gly Ala Ala Arg Ala Ser Gly Pro Arg Gly Gly Ala Pro Arg Gly Pro
    50                  55                  60
His Gly Gly Ala Ala Ser Ala Gln Asp Gly Arg Cys Pro Cys Gly Ala
65                  70                  75                  80
Arg Arg Pro Asp Ser Arg Leu Leu Glu Leu His Ile Thr Met Pro Phe
                85                  90                  95
Ser Ser Pro Met Glu Ala Glu Leu Val Arg Arg Ile Leu Ser Arg Asp
            100                 105                 110
Ala Ala Pro Leu Pro Arg Pro Gly Ala Val Leu Lys Asp Phe Thr Val
        115                 120                 125
Ser Gly Asn Leu Leu Phe Met Ser Val Trp Asp Gln Asp Arg Glu Gly
    130                 135                 140
Ala Gly Arg Met Arg Val Val Gly Trp Gly Leu Gly Ser Ala Ser Pro
145                 150                 155                 160
Glu Gly Gln Lys Ala Arg Asp Leu Arg Thr Pro Lys His Lys Val Ser
                165                 170                 175
Glu Gln Arg Pro Gly Thr Pro Gly Pro Pro Pro Pro Glu Gly Ala Gln
            180                 185                 190
Gly Asp Gly Cys Arg Gly Val Ala Phe Asn Val Met Phe Ser Ala Pro
        195                 200                 205
His Ile
    210


<210> 77
<211> 509
<212> PRT
<213> Homo sapiens

<400> 77
Met Glu Arg Arg Arg Leu Trp Gly Ser Ile Gln Ser Arg Tyr Ile Ser
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Met Ser Val Trp Thr Ser Pro Arg Arg Leu Val Glu Leu Ala Gly Gln
            20                  25                  30
Ser Leu Leu Lys Asp Glu Ala Leu Ala Ile Ala Ala Leu Glu Leu Leu
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        35                      40                      45
Pro Arg Glu Leu Phe Pro Pro Leu Phe Met Ala Ala Phe Asp Gly Arg
    50                      55                      60
His Ser Gln Thr Leu Lys Ala Met Val Gln Ala Trp Pro Phe Thr Cys
65                      70                      75                  80
Leu Pro Leu Gly Val Leu Met Lys Gly Gln His Leu His Leu Glu Thr
                85                      90                      95
Phe Lys Ala Val Leu Asp Gly Leu Asp Val Leu Leu Ala Gln Glu Val
            100                     105                     110
Arg Pro Arg Arg Trp Lys Leu Gln Val Leu Asp Leu Arg Lys Asn Ser
        115                     120                     125
His Gln Asp Phe Trp Thr Val Trp Ser Gly Asn Arg Ala Ser Leu Tyr
    130                     135                     140
Ser Phe Pro Glu Pro Glu Ala Ala Gln Pro Met Thr Lys Lys Arg Lys
145                     150                     155                 160
Val Asp Gly Leu Ser Thr Glu Ala Glu Gln Pro Phe Ile Pro Val Glu
                165                     170                     175
Val Leu Val Asp Leu Phe Leu Lys Glu Gly Ala Cys Asp Glu Leu Phe
            180                     185                     190
Ser Tyr Leu Ile Glu Lys Val Lys Arg Lys Lys Asn Val Leu Arg Leu
        195                     200                     205
Cys Cys Lys Lys Leu Lys Ile Phe Ala Met Pro Met Gln Asp Ile Lys
    210                     215                     220
Met Ile Leu Lys Met Val Gln Leu Asp Ser Ile Glu Asp Leu Glu Val
225                     230                     235                 240
Thr Cys Thr Trp Lys Leu Pro Thr Leu Ala Lys Phe Ser Pro Tyr Leu
                245                     250                     255
Gly Gln Met Ile Asn Leu Arg Arg Leu Leu Leu Ser His Ile His Ala
            260                     265                     270
Ser Ser Tyr Ile Ser Pro Glu Lys Glu Glu Gln Tyr Ile Ala Gln Phe
        275                     280                     285
Thr Ser Gln Phe Leu Ser Leu Gln Cys Leu Gln Ala Leu Tyr Val Asp
    290                     295                     300
Ser Leu Phe Phe Leu Arg Gly Arg Leu Asp Gln Leu Leu Arg His Val
305                     310                     315                 320
Met Asn Pro Leu Glu Thr Leu Ser Ile Thr Asn Cys Arg Leu Ser Glu
                325                     330                     335
Gly Asp Val Met His Leu Ser Gln Ser Pro Ser Val Ser Gln Leu Ser
            340                     345                     350
Val Leu Ser Leu Ser Gly Val Met Leu Thr Asp Val Ser Pro Glu Pro
        355                     360                     365
Leu Gln Ala Leu Leu Glu Arg Ala Ser Ala Thr Leu Gln Asp Leu Val
    370                     375                     380
Phe Asp Glu Cys Gly Ile Thr Asp Asp Gln Leu Leu Ala Leu Leu Pro
385                     390                     395                 400
Ser Leu Ser His Cys Ser Gln Leu Thr Thr Leu Ser Phe Tyr Gly Asn
                405                     410                     415
Ser Ile Ser Ile Ser Ala Leu Gln Ser Leu Leu Gln His Leu Ile Gly
            420                     425                     430
Leu Ser Asn Leu Thr His Val Leu Tyr Pro Val Pro Leu Glu Ser Tyr
        435                     440                     445
Glu Asp Ile His Gly Thr Leu His Leu Glu Arg Leu Ala Tyr Leu His
    450                     455                     460
Ala Arg Leu Arg Glu Leu Leu Cys Glu Leu Gly Arg Pro Ser Met Val
465                     470                     475                 480
Trp Leu Ser Ala Asn Pro Cys Pro His Cys Gly Asp Arg Thr Phe Tyr
                485                     490                     495
Asp Pro Glu Pro Ile Leu Cys Pro Cys Phe Met Pro Asn
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<210> 78
<211> 261
<212> PRT
<213> Homo sapiens

<400> 78
Met Trp Val Pro Val Val Phe Leu Thr Leu Ser Val Thr Trp Ile Gly
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Ala Ala Pro Leu Ile Leu Ser Arg Ile Val Gly Gly Trp Glu Cys Glu
20 25 30
Lys His Ser Gln Pro Trp Gln Val Leu Val Ala Ser Arg Gly Arg Ala
35 40 45
Val Cys Gly Gly Val Leu Val His Pro Gln Trp Val Leu Thr Ala Ala
50 55 60
His Cys Ile Arg Asn Lys Ser Val Ile Leu Leu Gly Arg His Ser Leu
65 70 75 80
Phe His Pro Glu Asp Thr Gly Gln Val Phe Gln Val Ser His Ser Phe
85 90 95
Pro His Pro Leu Tyr Asp Met Ser Leu Leu Lys Asn Arg Phe Leu Arg
100 105 110
Pro Gly Asp Asp Ser Ser His Asp Leu Met Leu Leu Arg Leu Ser Glu
115 120 125
Pro Ala Glu Leu Thr Asp Ala Val Lys Val Met Asp Leu Pro Thr Gln
130 135 140
Glu Pro Ala Leu Gly Thr Thr Cys Tyr Ala Ser Gly Trp Gly Ser Ile
145 150 155 160
Glu Pro Glu Glu Phe Leu Thr Pro Lys Lys Leu Gln Cys Val Asp Leu
165 170 175
His Val Ile Ser Asn Asp Val Cys Ala Gln Val His Pro Gln Lys Val
180 185 190
Thr Lys Phe Met Leu Cys Ala Gly Arg Trp Thr Gly Gly Lys Ser Thr
195 200 205
Cys Ser Gly Asp Ser Gly Gly Pro Leu Val Cys Asn Gly Val Leu Gln
210 215 220
Gly Ile Thr Ser Trp Gly Ser Glu Pro Cys Ala Leu Pro Glu Arg Pro
225 230 235 240
Ser Leu Tyr Thr Lys Val Val His Tyr Arg Lys Trp Ile Lys Asp Thr
245 250 255
Ile Val Ala Asn Pro
260

<210> 79
<211> 123
<212> PRT
<213> Homo sapiens

<400> 79
Met Lys Ala Val Leu Leu Ala Leu Leu Met Ala Gly Leu Ala Leu Gln
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Pro Gly Thr Ala Leu Leu Cys Tyr Ser Cys Lys Ala Gln Val Ser Asn
20 25 30
Glu Asp Cys Leu Gln Val Glu Asn Cys Thr Gln Leu Gly Glu Gln Cys
35 40 45
Trp Thr Ala Arg Ile Arg Ala Val Gly Leu Leu Thr Val Ile Ser Lys
50 55 60
Gly Cys Ser Leu Asn Cys Val Asp Asp Ser Gln Asp Tyr Tyr Val Gly
65 70 75 80
Lys Lys Asn Ile Thr Cys Cys Asp Thr Asp Leu Cys Asn Ala Ser Gly
85 90 95
Ala His Ala Leu Gln Pro Ala Ala Ala Ile Leu Ala Leu Leu Pro Ala

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<213> Homo sapiens

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<211> 2420

<212> DNA
<213> Homo sapiens

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<211> 4559
<212> DNA
<213> Homo sapiens

<400> 82
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<212> DNA
<213> Homo sapiens

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<211> 752
<212> DNA
<213> Homo sapiens

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<211> 2148
<212> DNA
<213> Homo sapiens

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<223> n = A,T,C or G

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<210> 86
<211> 1466
<212> DNA
<213> Homo sapiens

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<210> 87
<211> 990
<212> DNA
<213> Homo sapiens

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<221> misc_feature
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<223> n = A,T,C or G

<400> 87
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<211> 702
<212> PRT
<213> Homo sapiens

<400> 88
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35 40 45
Lys Glu Val Leu Leu Leu Val His Asn Leu Pro Gln His Leu Phe Gly
50 55 60
Tyr Ser Trp Tyr Lys Gly Glu Arg Val Asp Gly Asn Arg Gln Ile Ile
65 70 75 80
Gly Tyr Val Ile Gly Thr Gln Gln Ala Thr Pro Gly Pro Ala Tyr Ser
85 90 95
Gly Arg Glu Ile Ile Tyr Pro Asn Ala Ser Leu Leu Ile Gln Asn Ile
100 105 110
Ile Gln Asn Asp Thr Gly Phe Tyr Thr Leu His Val Ile Lys Ser Asp
115 120 125
Leu Val Asn Glu Glu Ala Thr Gly Gln Phe Arg Val Tyr Pro Glu Leu
130 135 140
Pro Lys Pro Ser Ile Ser Ser Asn Asn Ser Lys Pro Val Glu Asp Lys
145 150 155 160
Asp Ala Val Ala Phe Thr Cys Glu Pro Glu Thr Gln Asp Ala Thr Tyr
165 170 175
Leu Trp Trp Val Asn Asn Gln Ser Leu Pro Val Ser Pro Arg Leu Gln
180 185 190

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Arg Ser Asp Ser Val Ile Leu Asn Val Leu Tyr Gly Pro Asp Ala Pro
225                 230                 235                 240
Thr Ile Ser Pro Leu Asn Thr Ser Tyr Arg Ser Gly Glu Asn Leu Asn
                245                 250                 255
Leu Ser Cys His Ala Ala Ser Asn Pro Pro Ala Gln Tyr Ser Trp Phe
            260                 265                 270
Val Asn Gly Thr Phe Gln Gln Ser Thr Gln Glu Leu Phe Ile Pro Asn
        275                 280                 285
Ile Thr Val Asn Asn Ser Gly Ser Tyr Thr Cys Gln Ala His Asn Ser
    290                 295                 300
Asp Thr Gly Leu Asn Arg Thr Thr Val Thr Thr Ile Thr Val Tyr Ala
305                 310                 315                 320
Glu Pro Pro Lys Pro Phe Ile Thr Ser Asn Asn Ser Asn Pro Val Glu
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Asp Glu Asp Ala Val Ala Leu Thr Cys Glu Pro Glu Ile Gln Asn Thr
            340                 345                 350
Thr Tyr Leu Trp Trp Val Asn Asn Gln Ser Leu Pro Val Ser Pro Arg
        355                 360                 365
Leu Gln Leu Ser Asn Asp Asn Arg Thr Leu Thr Leu Leu Ser Val Thr
    370                 375                 380
Arg Asn Asp Val Gly Pro Tyr Glu Cys Gly Ile Gln Asn Glu Leu Ser
385                 390                 395                 400
Val Asp His Ser Asp Pro Val Ile Leu Asn Val Leu Tyr Gly Pro Asp
                405                 410                 415
Asp Pro Thr Ile Ser Pro Ser Tyr Thr Tyr Tyr Arg Pro Gly Val Asn
            420                 425                 430
Leu Ser Leu Ser Cys His Ala Ala Ser Asn Pro Pro Ala Gln Tyr Ser
        435                 440                 445
Trp Leu Ile Asp Gly Asn Ile Gln Gln His Thr Gln Glu Leu Phe Ile
    450                 455                 460
Ser Asn Ile Thr Glu Lys Asn Ser Gly Leu Tyr Thr Cys Gln Ala Asn
465                 470                 475                 480
Asn Ser Ala Ser Gly His Ser Arg Thr Thr Val Lys Thr Ile Thr Val
                485                 490                 495
Ser Ala Glu Leu Pro Lys Pro Ser Ile Ser Ser Asn Asn Ser Lys Pro
            500                 505                 510
Val Glu Asp Lys Asp Ala Val Ala Phe Thr Cys Glu Pro Glu Ala Gln
        515                 520                 525
Asn Thr Thr Tyr Leu Trp Trp Val Asn Gly Gln Ser Leu Pro Val Ser
    530                 535                 540
Pro Arg Leu Gln Leu Ser Asn Gly Asn Arg Thr Leu Thr Leu Phe Asn
545                 550                 555                 560
Val Thr Arg Asn Asp Ala Arg Ala Tyr Val Cys Gly Ile Gln Asn Ser
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Val Ser Ala Asn Arg Ser Asp Pro Val Thr Leu Asp Val Leu Tyr Gly
            580                 585                 590
Pro Asp Thr Pro Ile Ile Ser Pro Pro Asp Ser Ser Tyr Leu Ser Gly
        595                 600                 605
Ala Asn Leu Asn Leu Ser Cys His Ser Ala Ser Asn Pro Ser Pro Gln
    610                 615                 620
Tyr Ser Trp Arg Ile Asn Gly Ile Pro Gln Gln His Thr Gln Val Leu
625                 630                 635                 640
Phe Ile Ala Lys Ile Thr Pro Asn Asn Asn Gly Thr Tyr Ala Cys Phe
                645                 650                 655
Val Ser Asn Leu Ala Thr Gly Arg Asn Asn Ser Ile Val Lys Ser Ile
            660                 665                 670
Thr Val Ser Ala Ser Gly Thr Ser Pro Gly Leu Ser Ala Gly Ala Thr
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<211> 2974
<212> DNA
<213> Homo sapiens

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Ala Asp Glu Ala Val Lys Leu Gln Lys Glu Ile Asp Lys Arg Cys Gln
690 695 700
His Lys Ile Ala Glu Met Val Ala Leu Met Glu Lys His Lys His Gln
705 710 715 720
Tyr Asp Lys Ile Ile Glu Glu Arg Asp Ser Glu Leu Gly Leu Tyr Lys
725 730 735
Ser Lys Glu Gln Glu Gln Ser Ser Leu Arg Ala Ser Leu Glu Ile Glu
740 745 750
Leu Ser Asn Leu Lys Ala Glu Leu Leu Ser Val Lys Lys Gln Leu Glu
755 760 765
Ile Glu Arg Glu Glu Lys Glu Lys Leu Lys Arg Glu Ala Lys Glu Asn
770 775 780
Thr Ala Thr Leu Lys Glu Lys Lys Asp Lys Lys Thr Gln Thr Phe Leu
785 790 795 800
Leu Glu Thr Pro Glu Ile Tyr Trp Lys Leu Asp Ser Lys Ala Val Pro
805 810 815
Ser Gln Thr Val Ser Arg Asn Phe Thr Ser Val Asp His Gly Ile Ser
820 825 830
Lys Asp Lys Arg Asp Tyr Leu Trp Thr Ser Ala Lys Asn Thr Leu Ser
835 840 845
Thr Pro Leu Pro Lys Ala Tyr Thr Val Lys Thr Pro Thr Lys Pro Lys
850 855 860
Leu Gln Gln Arg Glu Asn Leu Asn Ile Pro Ile Glu Glu Ser Lys Lys
865 870 875 880

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Lys Arg Lys Met Ala Phe Glu Phe Asp Ile Asn Ser Asp Ser Ser Glu
                885                 890                 895
Thr Thr Asp Leu Leu Ser Met Val Ser Glu Glu Glu Thr Leu Lys Thr
            900                 905                 910
Leu Tyr Arg Asn Asn Asn Pro Pro Ala Ser His Leu Cys Val Lys Thr
        915                 920                 925
Pro Lys Lys Ala Pro Ser Ser Leu Thr Thr Pro Gly Pro Thr Leu Lys
    930                 935                 940
Phe Gly Ala Ile Arg Lys Met Arg Glu Asp Arg Trp Ala Val Ile Ala
945                 950                 955                 960
Lys Met Asp Arg Lys Lys Lys Leu Lys Glu Ala Glu Lys Leu Phe Val
                965                 970                 975


<210> 93
<211> 3393
<212> DNA
<213> Homo sapiens

<400> 93
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gttcgtacca ccgagatcaa gcagcagtca ggtgtctgcg gtgaaacctc agaccctggg 180
aggcgattcc actttcttca agagtttcaa caaatgtact gaagatgatt tggagtttcc 240
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gtataaggag gctgaaaaga taaaaaaatg gaaagtaagt acagaagctg aactgagaca 480
gaaagaaagt aagttgcaag aaaacagaaa gataattgaa gcacagcgaa aagccattca 540
ggaactgcaa tttggaaatg aaaaagtaag tttgaaatta gaagaaggaa tacaagaaaa 600
taaagattta ataaaagaga ataatgccac aaggcattta tgtaatctac tcaaagaaac 660
ctgtgctaga tctgcagaaa agacaaagaa atatgaatat gaacgggaag aaaccaggca 720
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tcttctccaa gccagagaga aagaagtaca tgatttggaa atacagttaa ctgccattac 1560
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aacccaatta agaaatgaac tagaatatgt gagagaagag ctaaaacaga aaagagatga 1860
agttaaatgt aaattggaca agagtgaaga aaattgtaac aatttaagga aacaagttga 1920
aaataaaaac aagtatattg aagaacttca gcaggagaat aaggccttga aaaaaaaagg 1980
tacagcagaa agcaagcaac tgaatgttta tgagataaag gtcaataaat tagagttaga 2040
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agaaagagaa gagaaggaaa aactcaaaag agaggcaaaa gaaaacacag ctactcttaa 2460
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tggcatatcc aaagataaaa gagactatct gtggacatct gccaaaaata ctttatctac 2640
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ttaactacat attgtctgga aacctgtcat tgtattcaga taattagatg attatatatt 3240
gttgttactt tttcttgtat tcatgaaaac tgtttttact aagttttcaa atttgtaaag 3300
ttagcctttg aatgctagga atgcattatt gagggtcatt ctttattctt tactattaaa 3360
atattttgga tgcaaaaaaa aaaaaaaaaa aaa 3393

<210> 94
<211> 188
<212> PRT
<213> Homo sapiens

<400> 94
Met Asn Gly Asp Asp Ala Phe Ala Arg Arg Pro Arg Asp Asp Ala Gln
1 5 10 15
Ile Ser Glu Lys Leu Arg Lys Ala Phe Asp Asp Ile Ala Lys Tyr Phe
20 25 30
Ser Lys Lys Glu Trp Glu Lys Met Lys Ser Ser Glu Lys Ile Val Tyr
35 40 45
Val Tyr Met Lys Leu Asn Tyr Glu Val Met Thr Lys Leu Gly Phe Lys
50 55 60
Val Thr Leu Pro Pro Phe Met Arg Ser Lys Arg Ala Ala Asp Phe His
65 70 75 80
Gly Asn Asp Phe Gly Asn Asp Arg Asn His Arg Asn Gln Val Glu Arg
85 90 95
Pro Gln Met Thr Phe Gly Ser Leu Gln Arg Ile Phe Pro Lys Ile Met
100 105 110
Pro Lys Lys Pro Ala Glu Glu Glu Asn Gly Leu Lys Glu Val Pro Glu
115 120 125
Ala Ser Gly Pro Gln Asn Asp Gly Lys Gln Leu Cys Pro Pro Gly Asn
130 135 140
Pro Ser Thr Leu Glu Lys Ile Asn Lys Thr Ser Gly Pro Lys Arg Gly
145 150 155 160
Lys His Ala Trp Thr His Arg Leu Arg Glu Arg Lys Gln Leu Val Val
165 170 175
Tyr Glu Glu Ile Ser Asp Pro Glu Glu Asp Asp Glu
180 185

<210> 95
<211> 576
<212> DNA
<213> Homo sapiens

<400> 95
atgaacggag acgacgcctt tgcaaggaga cccagggatg atgctcaaat atcagagaag 60
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aaatcctcgg agaaaatcgt ctatgtgtat atgaagctaa actatgaggt catgactaaa 180
ctaggtttca aggtcaccct cccacctttc atgcgtagta aacgggctgc agacttccac 240
gggaatgatt ttggtaacga tcgaaaccac aggaatcagg ttgaacgtcc tcagatgact 300
ttcggcagcc tccagagaat cttcccgaag atcatgccca agaagccagc agaggaagaa 360

aatggtttga aggaagtgcc agaggcatct ggcccacaaa atgatgggaa acagctgtgc 420
cccccgggaa atccaagtac cttggagaag attaacaaga catctggacc caaaaggggg 480
aaacatgcct ggacccacag actgcgtgag agaaagcagc tggtggttta tgaagagatc 540
agcgaccctg aggaagatga cgagtaactc ccctcg 576

<210> 96
<211> 94
<212> PRT
<213> Homo sapiens

<400> 96
Pro Ala Thr Gln Arg Gln Asp Pro Ala Ala Ala Gln Glu Gly Glu Asp
1 5 10 15
Glu Gly Ala Ser Ala Gly Gln Gly Pro Lys Pro Glu Ala Asp Ser Gln
20 25 30
Glu Gln Gly His Pro Gln Thr Gly Cys Glu Cys Glu Asp Gly Pro Asp
35 40 45
Gly Gln Glu Met Asp Pro Pro Asn Pro Glu Glu Val Lys Thr Pro Glu
50 55 60
Glu Glu Met Arg Ser His Tyr Val Ala Gln Thr Gly Ile Leu Trp Leu
65 70 75 80
Leu Met Asn Asn Cys Phe Leu Asn Leu Ser Pro Arg Lys Pro
85 90

<210> 97
<211> 646
<212> DNA
<213> Homo sapiens

<400> 97
ctgccgtccg gactcttttt cctctactga gattcatctg tgtgaaatat gagttggcga 60
ggaagatcga cctatcggcc tagaccaaga cgctacgtag agcctcctga aatgattggg 120
cctatgcggc ccgagcagtt cagtgatgaa gtggaaccag caacacctga agaaggggaa 180
ccagcaactc aacgtcagga tcctgcagct gctcaggagg gagaggatga gggagcatct 240
gcaggtcaag ggccgaagcc tgaagctgat agccaggaac agggtcaccc acagactggg 300
tgtgagtgtg aagatggtcc tgatgggcag gagatggacc cgccaaatcc agaggaggtg 360
aaaacgcctg aagaagagat gaggtctcac tatgttgccc agactgggat tctctggctt 420
ttaatgaaca attgcttctt aaatctttcc ccacggaaac cttgagtgac tgaaatatca 480
aatggcgaga gaccgtttag ttcctatcat ctgtggcatg tgaagggcaa tcacagtgtt 540
aaaagaagac atgctgaaat gttgcaggct gctcctatgt tggaaaattc ttcattgaag 600
ttctcccaat aaagctttac agccttctgc aaagaaaaaa aaaaaa 646

<210> 98
<211> 98
<212> PRT
<213> Homo sapiens

<400> 98
His Cys Pro Thr Glu Asn Glu Pro Asp Leu Ala Gln Cys Phe Phe Cys
1 5 10 15
Phe Lys Glu Leu Glu Gly Trp Glu Pro Asp Asp Asp Pro Ile Glu Glu
20 25 30
His Lys Lys His Ser Ser Gly Cys Ala Phe Leu Ser Val Lys Lys Gln
35 40 45
Phe Glu Glu Leu Thr Leu Gly Glu Phe Leu Lys Leu Asp Arg Glu Arg
50 55 60
Ala Lys Asn Lys Ile Ala Lys Glu Thr Asn Asn Lys Lys Lys Glu Phe
65 70 75 80
Glu Glu Thr Ala Lys Lys Val Arg Arg Ala Ile Glu Gln Leu Ala Ala
85 90 95

Met Asp

<210> 99
<211> 1619
<212> DNA
<213> Homo sapiens

<400> 99
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ctggcccttc ttggagggct gcgcctgcac cccggagcgg atggccgagg ctggcttcat 180
ccactgcccc actgagaacg agccagactt ggcccagtgt ttcttctgct tcaaggagct 240
ggaaggctgg gagccagatg acgaccccat agaggaacat aaaaagcatt cgtccggttg 300
cgctttcctt tctgtcaaga agcagtttga agaattaacc cttggtgaat tttgaaact 360
ggacagagaa agagccaaga acaaaattgc aaaggaaacc aacaataaga agaaagaatt 420
tgaggaaact gcgaagaaag tgcgccgtgc catcgagcag ctggctgcca tggattgagg 480
cctctggccg gagctgcctg gtcccagagt ggctgcacca cttccagggt ttattccctg 540
gtgccaccag ccttcctgtg ggccccttag caatgtctta ggaaaggaga tcaacatttt 600
caaattagat gtttcaactg tgctcctgtt ttgtcttgaa agtggcacca gaggtgcttc 660
tgcctgtgca gcgggtgctg ctggtaacag tggctgcttc tctctctctc tctcttttt 720
gggggctcat ttttgctgtt ttgattcccg ggcttaccag gtgagaagtg agggaggaag 780
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ggtgcctgtt gaatctgagc tgcaggttcc ttatctgtca cacctgtgcc tcctcagagg 960
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gtgatgagag aatggagaca gagtccctgg ctcctctact gtttaacaac atggctttct 1080
tattttgttt gaattgttaa ttcacagaat agcacaaact acaattaaaa ctaagcacaa 1140
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gatggatttg attcgccctc ctccctgtca tagagctgca gggtggattg ttacagcttc 1560
gctggaaacc tctggaggtc atctcggctg ttcctgagaa ataaaaagcc tgtcatttc 1619

<210> 100
<211> 74
<212> PRT
<213> Homo sapiens

<400> 100
Cys Trp Tyr Cys Arg Arg Arg Asn Gly Tyr Arg Ala Leu Met Asp Lys
1 5 10 15
Ser Leu His Val Gly Thr Gln Cys Ala Leu Thr Arg Arg Cys Pro Gln
20 25 30
Glu Gly Phe Asp His Arg Asp Ser Lys Val Ser Leu Gln Glu Lys Asn
35 40 45
Cys Glu Pro Val Val Pro Asn Ala Pro Pro Ala Tyr Glu Lys Leu Ser
50 55 60
Ala Glu Gln Ser Pro Pro Pro Tyr Ser Pro
65 70

<210> 101
<211> 1524
<212> DNA
<213> Homo sapiens

<400> 101
agcagacaga ggactctcat taaggaaggt gtcctgtgcc ctgaccctac aagatgccaa 60
gagaagatgc tcacttcatc tatggttacc ccaagaaggg gcacggccac tcttacacca 120
cggctgaaga ggccgctggg atcggcatcc tgacagtgat cctgggagtc ttactgctca 180
tcggctgttg gtattgtaga agacgaaatg gatacagagc cttgatggat aaaagtcttc 240
atgttggcac tcaatgtgcc ttaacaagaa gatgcccaca agaagggttt gatcatcggg 300
acagcaaagt gtctcttcaa gagaaaaact gtgaacctgt ggttcccaat gctccacctg 360
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gacacctgag acatgctgaa attatttctc tcacactttt gcttgaattt aatacagaca 480
tctaatgttc tcctttggaa tggtgtagga aaaatgcaag ccatctctaa taataagtca 540
gtgttaaaat tttagtaggt ccgctagcag tactaatcat gtgaggaaat gatgagaaat 600
attaaattgg gaaaactcca tcaataaatg ttgcaatgca tgatactatc tgtgccagag 660
gtaatgttag taaatccatg gtgttatttt ctgagagaca gaattcaagt gggtattctg 720
gggccatcca atttctcttt acttgaaatt tggctaataa caaactagtc aggttttcga 780
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aataagtaaa agctactatg tactgcctta gtgctgatgc ctgtgtactg ccttaaatgt 1440
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aatcataaag gatcagagat tctg 1524

<210> 102
<211> 43
<212> PRT
<213> Homo sapiens

<400> 102
Met Ala Ala Arg Ala Val Phe Leu Ala Leu Ser Ala Gln Leu Leu Gln
1 5 10 15
Ala Arg Leu Met Lys Glu Glu Ser Pro Val Val Ser Trp Arg Leu Glu
20 25 30
Pro Glu Asp Gly Thr Ala Leu Cys Phe Ile Phe
35 40

<210> 103
<211> 1004
<212> DNA
<213> Homo sapiens

<400> 103
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aggagaaggg ggagctggag gctggagcct gtaacaccgt ggctcgtctc actctggatg 120
gtggtggcaa cagagatggc agcgcagctg gagtgttagg agggcggcct gagcggtagg 180
agtggggctg gagcagtaag atggcggcca gagcggtttt tctggcattg tctgcccagc 240
tgctccaagc caggctgatg aaggaggagt cccctgtggt gagctggagg ttggagcctg 300
aagacggcac agctctgtgc ttcatcttct gaggttgtgg cagccacggt gatggagacg 360
gcagctcaac aggagcaata ggaggagatg gagtttcact gtgtcagcca ggatggtctc 420
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tgtatcatta tccttgtgct gcaggagccg gctcctttca ggatttcagt cacatcttcc 600
tgctttgtcc agaacacatt gaccaagctc ctgaaagatg taagtttact acgcatagac 660
ttttaaactt caaccaatgt atttactgaa aataacaaat gttgtaaatt ccctgagtgt 720
tattctactt gtattaaaag gtaataatac ataatcatta aaatctgagg gatcattgcc 780

agagattgtt ggggagggaa atgttatcaa cggtttcatt gaaattaaat ccaaaaagtt 840
atttcctcag aaaaatcaaa taaagtttgc atgtttttta ttcttaaaac attttaaaaa 900
ccactgtaga atgatgtaaa tagggactgt gcagtatttc tgacatatac tataaaatta 960
ttaaaaagtc aatcagtatt caacatcttt tacactaaaa agcc 1004

<210> 104
<211> 9
<212> PRT
<213> Homo sapiens

<400> 104
Trp Val Leu Thr Ala Ala His Cys Ile
1 5

<210> 105
<211> 263
<212> PRT
<213> Homo sapiens

<400> 105
Pro Met Trp Phe Leu Val Leu Cys Leu Ala Leu Ser Leu Gly Gly Thr
1 5 10 15
Gly Ala Ala Pro Pro Ile Gln Ser Arg Ile Val Gly Gly Trp Glu Cys
20 25 30
Glu Gln His Ser Gln Pro Trp Gln Ala Ala Leu Tyr His Phe Ser Thr
35 40 45
Phe Gln Cys Gly Gly Ile Leu Val His Arg Gln Trp Val Leu Thr Ala
50 55 60
Ala His Cys Ile Ser Asp Asn Tyr Gln Leu Trp Leu Gly Arg His Asn
65 70 75 80
Leu Phe Asp Asp Glu Asn Thr Ala Gln Phe Val His Val Ser Glu Ser
85 90 95
Phe Pro His Pro Gly Phe Asn Met Ser Leu Leu Glu Asn His Thr Arg
100 105 110
Gln Ala Asp Glu Asp Tyr Ser His Asp Leu Met Leu Leu Arg Leu Thr
115 120 125
Glu Pro Ala Asp Thr Ile Thr Asp Ala Val Lys Val Val Glu Leu Pro
130 135 140
Thr Gln Glu Pro Glu Val Gly Ser Thr Cys Leu Ala Ser Gly Trp Gly
145 150 155 160
Ser Ile Glu Pro Glu Asn Phe Ser Phe Pro Asp Asp Leu Gln Cys Val
165 170 175
Asp Leu Lys Ile Leu Pro Asn Asp Glu Cys Glu Lys Ala His Val Gln
180 185 190
Lys Val Thr Asp Phe Met Leu Cys Val Gly His Leu Glu Gly Gly Lys
195 200 205
Asp Thr Cys Val Gly Asp Ser Gly Gly Pro Leu Met Cys Asp Gly Val
210 215 220
Leu Gln Gly Val Thr Ser Trp Gly Tyr Val Pro Cys Gly Thr Pro Asn
225 230 235 240
Lys Pro Ser Val Ala Val Arg Val Leu Ser Tyr Val Lys Trp Ile Glu
245 250 255
Asp Thr Ile Ala Glu Asn Ser
260

<210> 106
<211> 270
<212> PRT
<213> Homo sapiens

<400> 106
Pro Met Ile Arg Thr Leu Leu Leu Ser Thr Leu Val Ala Gly Ala Leu
1 5 10 15
Ser Cys Gly Asp Pro Thr Tyr Pro Pro Tyr Val Thr Arg Val Val Gly
20 25 30
Gly Glu Glu Ala Arg Pro Asn Ser Trp Pro Trp Gln Val Ser Leu Gln
35 40 45
Tyr Ser Ser Asn Gly Lys Trp Tyr His Thr Cys Gly Gly Ser Leu Ile
50 55 60
Ala Asn Ser Trp Val Leu Thr Ala Ala His Cys Ile Ser Ser Ser Arg
65 70 75 80
Thr Tyr Arg Val Gly Leu Gly Arg His Asn Leu Tyr Val Ala Glu Ser
85 90 95
Gly Ser Leu Ala Val Ser Val Ser Lys Ile Val Val His Lys Asp Trp
100 105 110
Asn Ser Asn Gln Ile Ser Lys Gly Asn Asp Ile Ala Leu Leu Lys Leu
115 120 125
Ala Asn Pro Val Ser Leu Thr Asp Lys Ile Gln Leu Ala Cys Leu Pro
130 135 140
Pro Ala Gly Thr Ile Leu Pro Asn Asn Tyr Pro Cys Tyr Val Thr Gly
145 150 155 160
Trp Gly Arg Leu Gln Thr Asn Gly Ala Val Pro Asp Val Leu Gln Gln
165 170 175
Gly Arg Leu Leu Val Val Asp Tyr Ala Thr Cys Ser Ser Ser Ala Trp
180 185 190
Trp Gly Ser Ser Val Lys Thr Ser Met Ile Cys Ala Gly Gly Asp Gly
195 200 205
Val Ile Ser Ser Cys Asn Gly Asp Ser Gly Gly Pro Leu Asn Cys Gln
210 215 220
Ala Ser Asp Gly Arg Trp Gln Val His Gly Ile Val Ser Phe Gly Ser
225 230 235 240
Arg Leu Gly Cys Asn Tyr Tyr His Lys Pro Ser Val Phe Thr Arg Val
245 250 255
Ser Asn Tyr Ile Asp Trp Ile Asn Ser Val Ile Ala Asn Asn
260 265 270

<210> 107
<211> 270
<212> PRT
<213> Homo sapiens

<400> 107
Pro Met Ile Arg Thr Leu Leu Leu Ser Thr Leu Val Ala Gly Ala Leu
1 5 10 15
Ser Cys Gly Val Ser Thr Tyr Ala Pro Asp Met Ser Arg Met Leu Gly
20 25 30
Gly Glu Glu Ala Arg Pro Asn Ser Trp Pro Trp Gln Val Ser Leu Gln
35 40 45
Tyr Ser Ser Asn Gly Gln Trp Tyr His Thr Cys Gly Gly Ser Leu Ile
50 55 60
Ala Asn Ser Trp Val Leu Thr Ala Ala His Cys Ile Ser Ser Ser Arg
65 70 75 80
Ile Tyr Arg Val Met Leu Gly Gln His Asn Leu Tyr Val Ala Glu Ser
85 90 95
Gly Ser Leu Ala Val Ser Val Ser Lys Ile Val Val His Lys Asp Trp
100 105 110
Asn Ser Asn Gln Val Ser Lys Gly Asn Asp Ile Ala Leu Leu Lys Leu
115 120 125
Ala Asn Pro Val Ser Leu Thr Asp Lys Ile Gln Leu Ala Cys Leu Pro

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Trp Gly Arg Leu Gln Thr Asn Gly Ala Leu Pro Asp Asp Leu Lys Gln
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Gly Arg Leu Leu Val Val Asp Tyr Ala Thr Cys Ser Ser Ser Gly Trp
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Trp Gly Ser Thr Val Lys Thr Asn Met Ile Cys Ala Gly Gly Asp Gly
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Val Ile Cys Thr Cys Asn Gly Asp Ser Gly Gly Pro Leu Asn Cys Gln
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Ala Ser Asp Gly Arg Trp Glu Val His Gly Ile Gly Ser Leu Thr Ser
225                 230                 235                 240
Val Leu Gly Cys Asn Tyr Tyr Tyr Lys Pro Ser Ile Phe Thr Arg Val
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Asn

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Arg Leu Met Lys Glu Glu Ser Pro Val Val
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